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A Matter of Composition

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Many new drug substances can be classified according to the Biopharmaceutical Classification System (BCS) as class II drugs. These drugs show a poor aqueous solubility but once dissolved they are rapidly absorbed over the gastro-intestinal membrane. Therefore, the dissolution rate of the drug determines its bioavailability after oral administration. The application of solid dispersion is a promising approach to increase the dissolution rate of these drugs. A solid dispersion is generally composed of a drug incorporated in a (hydrophilic) carrier or matrix. The drug can be present in the amorphous state and/or as small crystals. An increased dissolution rate of the drugs incorporated in the solid dispersion is attributed to an increased surface area available for dissolution, an increased saturation concentration of the drug, a decreased thickness of the diffusion layer and an increased wettability of the drug. Two essential factors that strongly influence the dissolution behavior of solid dispersions are their composition and the method used to produce them. The next to the BCS class II drugs BCS class IV drugs may also benefit from the use of solid dispersions. The bioavailability of class IV drugs is limited because of both a poor solubility as well as a poor permeability. Although in general the improved dissolution rate will not improve the poor permeability, the overall bioavailability of these drugs may increase due to the improved dissolution behavior provided by the solid dispersions.

The aims of this thesis are to investigate the influence of the type of carrier and other excipients incorporated the solid dispersions on dissolution behavior of solid dispersion tablets, and to study their physical stability. The solid dispersions investigated in this thesis were prepared by either freeze drying or spray freeze drying.

In **Chapter 2**, we reviewed the most currently used methods to produce solid dispersions, i.e. the fusion method, hot melt extrusion, spray drying, freeze drying or supercritical fluid drying described in literature. In addition, the physico-chemical characteristics of the obtained solid dispersions are discussed in relation to their production process. Furthermore, advantages and disadvantages of the production methods are discussed.

In **Chapter 3**, we investigated the dissolution behavior of solid dispersion tablets containing the two different carriers (inulin versus polyvinylpyrrolidone (PVP)). Inulin, an oligosaccharide, was recently introduced as an alternative as carrier for solid dispersions. Therefore, we considered it interesting to compare it with a widely used carrier, i.e. PVP. Freeze drying was used to prepare the solid dispersions and diazepam and nifedipine were used as model drugs. Modulated differential scanning calorimetry (MDSC) and X-ray powder diffractrometry (XRPD) were used to characterize the solid state of the drug incorporated in the carriers. Moreover, the solubility of the drugs in aqueous solutions of the carriers was determined to investigate whether or not the drugs can interact with the carriers. The dissolution behavior of tablets prepared from the solid dispersions was investigated. To obtain a better understanding of the

mechanisms of dissolution of the different dispersions, the dissolution rate of both drug and carrier were determined.

In **Chapter 4**, we investigated the effect of the incorporation of a superdisintegrant in solid dispersion tablet on its dissolution behavior. The following aspects were studied: i) the mode of superdisintegrant incorporation in the solid dispersion tablets (physically mixed or incorporated in the solid dispersion), ii) the type of superdisintegrant (sodium starch glycolate (Primojel®), croscarmellose sodium (Ac-Di-Sol®), crosslinked-PVP (Polyplasdone®XL and XL-10) and iii) the type of carrier (inulin, PVP, polyethylene glycol, hydroxypropyl-β-cyclodextrin and mannitol). The solid dispersions were prepared by freeze drying, and fenofibrate was used as a model drug. DSC and XRPD were used to characterize the solid state of the drugs incorporated in the carriers. Moreover, the dissolution behavior of the tablets prepared from the solid dispersions was investigated. Besides the dissolution behavior, also the disintegration rate of the solid dispersion tablets was investigated. Furthermore, the dissolution behavior of some selected solid dispersion tablets stored at 20°C/45%RH and 40°C/75%RH for 3 months was studied. Finally, the dissolution behavior of the best performing solid dispersion tablet formulation was compared to that of a commercial product containing nanocrystals (Lipanthyl® tablets).

In **Chapter 5**, we investigated the applicability of a new surface-active derivative of inulin (Inutec®SP1) as a carrier for solid dispersions by comparing it with native inulin and PVP. Four different drugs were used (diazepam, fenofibrate, ritonavir and efavirenz) and solid dispersions were prepared by spray freeze drying. The dissolution behavior of solid dispersion tablets containing the different carriers was studied. Surface tension of aqueous carrier solutions, and the solubility of the drugs in the different carrier solutions were measured to determine the surface activity of the carriers, and to investigate whether or not the drugs can interact with the carriers, respectively. MDSC, scanning electron microscope (SEM) and water vapor sorption (DVS) were used to characterize the solid state of the drugs incorporated in the carriers. In addition, the dissolution behavior of Inutec®SP1-based solid dispersion tablets stored at 20°C/45%RH and 40°C/75%RH for 3 months was investigated.

In **Chapter 6**, we developed a tacrolimus tablet for sublingual administration. A motivation of this study came from the observation that after oral administration, tacrolimus exhibited a low bioavailability and a high variation of plasma levels between patients. These phenomena were attributed to the low aqueous solubility of tacrolimus and the first pass metabolism in liver. Therefore, the use of solid dispersion technique combined with a new route of drug administration might improve bioavailability and reduce variations in plasma levels. Tacrolimus was incorporated in three different carries, i.e. inulin 1.8 kDa and 4 kDa, and PVP K30 at drug loads of 2.5%, 5% and 10% w/w by freeze drying. Furthermore, the superdisintegrant (Ac-Di-Sol®) was incorporated in the solid dispersions at a concentration of 4% w/w. SEM and XRPD were used to characterize the solid state of the drug in the carriers. The solid dispersions

were further formulated to produce the tablets weighing 75 mg and containing 1 mg of tacrolimus. The additional tablet excipients were Ac-Di-Sol®, mannitol, sodium stearyl fumarate and Avicel® PH-101 and they were physically mixed with the solid dispersions. The dissolution behavior and the disintegration time of the tablets were determined. In addition, the storage stability at 20°C/45%RH and 40°C/75%RH of the optimized tablet formulation was investigated.

CHAPTER 2

IMPROVED DISSOLUTION BEHAVIOR OF LIPOPHILIC DRUGS BY SOLID DISPERSIONS: FORMULATION CONSIDERATIONS RELATED TO THE PRODUCTION PROCESS

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2.1 ABSTRACT

Importance of the field: Many new drug substances have a low aqueous solubility which can cause a poor bioavailability after oral administration. Application of solid dispersions is a useful method to increase the dissolution rate of these drugs and thereby improve their bioavailability. So far, several methods have been developed to prepare solid dispersions. To obtain a product with the desired quality attributes, both the formulation and production process should be considered in the design and development of the product.

Area covered in this review: Most currently used methods to produce solid dispersions, like the fusion method, hot melt extrusion, spray drying, freeze drying or supercritical fluid drying, are reviewed. In addition, the physico-chemical characteristics of the obtained solid dispersions are discussed.

What the reader will gain: Important formulation and production aspects, and the advantages/ disadvantages of each production method are presented.

Take home message: Solid dispersions can be successfully prepared by the currently available methods. Both processes and formulation aspects strongly affect the characteristics of solid dispersion products. An increased dissolution rate and improved bioavailability after oral administration of various lipophilic drugs through the use of solid dispersions has been demonstrated in several studies.

2.2 ARTICLE HIGHLIGHTS

» Fusion is the most simple method to produce solid dispersion and is therefore useful for screening formulations.
» Hot melt extrusion is a promising method. The method can be applied to various drugs. Application of synthetic polymers as carrier in solid dispersions is preferred for this method.
» Spray drying and freeze drying are frequently applied methods to produce solid dispersions. The type of solvents used strongly influences the characteristics of the final solid dispersions such as powder morphology, physical state of the component in the solid dispersion and dissolution rate of the drug.
» Supercritical fluid drying is a more recent method to prepare solid dispersions. The solubility of drug and carrier in the supercritical fluids, and the miscibility of solvent and supercritical fluids are the key factors in the production process.
» The physical state of the components in solid dispersions, and dissolution rate are determined by the production method, the production conditions, the type of carriers and the drug load.

2.3 INTRODUCTION

Bioavailability refers to the extent and rate at which a drug reaches the systemic circulation after administration. When the drug is administered via the intravenous route, the bioavailability is considered to be 100%. However, most of the drugs are administered via other routes, such as the oral route, due to poor dissolution, the incapability to permeate the absorbing membrane or metabolic transformation during the absorption process the bioavailability of these drugs is often incomplete. Several drugs yield erratic absorption after oral administration caused by incomplete dissolution in the gastrointestinal (GI) lumen when administered as solid dosage form

The Biopharmaceutics Classification System (BCS) is used for correlating *in vitro* drug dissolution and *in vivo* bioavailability following oral administration. Solubility and permeability (including metabolic transformation) of drugs are essential parameters determining bioavailability. Consequently, drugs can be classified into four groups as shown in Table 1 [1]. BCS class II drugs are of specific interest, because the number of poorly water-soluble compounds rapidly increases in drug discovery [2]. Permeability of BCS class II drugs over the intestinal membrane is fast and hence the absorption will mainly be determined by the dissolution rate of the drug in the GI fluids. Therefore, ways to enhance the dissolution rate of poorly water-soluble drugs becomes a challenge. Application of solid dispersions is an approach which has been used to enhance the dissolution rate of these drugs. Solid dispersions are generally systems in which the drug is incorporated in an inert hydrophilic carrier. The solid state of drugs in the solid dispersions can be amorphous and/or crystalline. When the drug is in the amorphous state, it can be incorporated in the solid dispersion as

Table 1 Biopharmaceuticals Classification System.

Class	Solubility	Permeability	Examples of drug
I	High	High	cyclophosphamide, pyrazinamide, stavudine, zidovudine
II	Low	High	dapsone, griseofulvin, phenytoin, nifedipine
III	High	Low	atenolol, colchicine, cimetidine, hydrochlorothiazide
IV	Low	Low	furosemide, indinavir, saquinavir, ritonavir

particles or dispersed over the carrier at a molecular level. However, when the drug is in the crystalline state, it is incorporated as particles only. Theoretically, the drug could form mixed crystals with the carrier. However, to our knowledge, such mixed crystals have never been encountered with solid dispersions. When the drug is incorporated in the solid dispersion as particles, the size of these particles is usually in the nano-size range. The very small particles result in an increased dissolution rate which can be explained by the Noyes-Whitney equation [3]:

$$\frac{dm}{dt} = \frac{D * A}{h}(C_s - C_{bulk}) \tag{1}$$

where dm/dt is the dissolution rate of drug, D is the diffusion coefficient of drug, A is the surface area of the drug, C_s is the saturation concentration of the drug, C_{bulk} is the concentration of drug in the bulk, and h is the thickness of the hydrodynamic boundary layer.

The very small particle size results in a large surface area (A) and thus in an increased dissolution rate. In addition, very small (nano-sized) particles do not only result in a large surface area (A), but also in an increased saturation concentration (C_s) which can be derived from the Ostwald-Freundlich equation [4]:

$$C_{s,curve} = C_{s,flat} * \exp\left(\frac{2 * \gamma * M}{R * T * \rho * r}\right) \tag{2}$$

where $C_{s,curve}$ is the saturation concentration at a curved surface, $C_{s,flat}$ is the saturation concentration at a flat surface, γ is interfacial surface tension of the solid drug to solution interface, M is the molecular weight of drug, R is the gas constant, T is the temperature, ρ is the density of drug, finally r is the radius of curvature of the dissolving surface. The decreased radius of the curvature of the dissolving surface (r) results in the increased saturation concentration at the curved surface ($C_{s,curve}$) and thereby in an increased dissolution rate.

Moreover, the very small particle also results in a decreased thickness of the hydrodynamic boundary layer (h) in equation (1) which can be explained by the Prandtl boundary layer equation [5]:

$$h = k * \frac{\sqrt{L}}{\sqrt{V}} \quad (3)$$

where h is the thickness of hydrodynamic boundary layer, k is a constant, L is the length of the surface in the direction of flow, and V is the relative velocity of the flowing liquid versus the flat surface. The decreased particle size results in a decreased length of the surface in the direction of flow (L) and thus in a decreased thickness of hydrodynamic boundary layer (h). In equation (1), the decrease in the thickness of hydrodynamic boundary layer (h) yields an increased dissolution rate.

In addition, when the drug is incorporated in the amorphous state, it has a higher solubility (C_s) than when the drug is crystalline which results in a higher dissolution rate [6]. Finally, since the drug in the solid dispersion is in intimate contact with the hydrophilic carrier, its wetability is improved resulting in an increased dissolution rate [7].

Most solid dispersions exist as glass solutions, glass suspensions or fully crystalline dispersions. A glass solution is a system in which the drug is dispersed in an amorphous carrier on a molecular level. However, because the amorphous state has a higher Gibbs energy than the crystalline state, a glass solution is thermodynamically unstable. Consequently, both drug and carrier may be prone to crystallization during storage. A change of the physical state of drug and/or carrier is highly unwanted since it may affect the dissolution behavior of the solid dispersions. Hydrophilic carriers with high glass transition temperatures (T_gs) are used in order to improve the kinetic stability of the glass solutions. Examples of carriers with a high T_g are polyvinylpyrrolidone (PVP) [8,9] or hydroxypropyl methylcellulose (HPMC) [10,11] and inulin [12]. In general, it is rather difficult to prepare glass solutions with a high drug load without the formation of drug clusters, which may limit the application of this system to relatively low-dosed drugs.

A glass suspension can be described as a system in which a drug is dispersed as amorphous clusters in an amorphous carrier. Usually, the drug is also partially dispersed in the carrier on a molecular level. This type of solid dispersion is usually found when the drug load is high. For example, it has been found that diazepam incorporated in inulin solid dispersions at a drug load of 35% w/w partially existed as amorphous clusters and was partially dispersed in the carrier at a molecular level [12]. A disadvantage of a glass suspension is that after processing and/or after storage, the drug in the amorphous clusters may be prone to crystallization, in particular when the drug has a low T_g. For instance, it has been found that fenofibrate (T_g = -19.6°C) incorporated in PVP, inulin or hydroxypropyl-β-cyclodextrin (HPβCD) at a drug load of 50% w/w was partially crystalline and partially in the amorphous state [13].

A fully crystalline dispersion is a system in which small drug crystals are intimately dispersed in a crystalline carrier. Since the drug is in the crystalline state, its physical stability is better than its amorphous counterpart. However, the solubility and dissolution

rate of drug in crystalline state is lower than that in the amorphous state. In order to maintain still a fast dissolution rate, the preparation of fully crystalline dispersions containing nano-sized drug particles has become a fascinating challenge. For example, a crystalline dispersion of fenofibrate incorporated in polyethylene glycol (PEG) 8000 was investigated. Both fenofibrate and PEG readily crystallize because of their very low $T_g s$. The particle size of fenofibrate in PEG was less than 10 μm whereas particle size of unprocessed fenofibrate was 100 μm [14]. Other drug substances dispersed in PEG in the crystalline state that have been reported are for example ibuprofen [15], ofloxacin [16], nifedipine [17] and flurbiprofen [18].

The type of solid dispersion and its dissolution behavior are strongly influenced by the physicochemical properties of drug and carrier, and the used production process. This review focuses on techniques widely used for preparing solid dispersions (thermal and solvent methods). Furthermore, process and formulation aspects affecting the type of solid dispersion that is obtained are described. In addition, critical concerns and advantages/disadvantages of the methods are discussed.

2.4 PREPARATION OF SOLID DISPERSIONS

2.4.1 Thermal method

2.4.1.1 Simple fusion

The fusion method refers to a process in which a drug is dissolved in one or more molten carriers or carriers in the rubbery state and then cooled under stirring to form a solid dispersion. Alternatively, the drug is first dissolved in a solvent and then transferred into a molten carrier. Subsequently the solvent is evaporated by heat. After solidification, the solid mass is milled, extruded and/or sieved in order to obtain a powder. The fusion method is a very simple process. It may be useful for screening of formulations. Nevertheless, one major disadvantage of this method is that the texture of the solid dispersion after cooling is quite hard. Therefore, size reduction of the solid dispersion may be difficult. Factors that can influence dissolution behavior of drug are the type of carrier, the cooling rate and the final temperature.

The most important requirement with this method is that drug and carrier should be stable at the process temperature. In general, carriers should have a lower melting point (T_m) or T_g than the drug to allow a more practically processing temperature and to decrease the potential of drug degradation. Many carriers have been used such as mannitol, PEGs and poloxamers. PEGs are mostly used for this method because they have a low melting point of about 37°C to 63°C, depending on its molecular weight. In addition, many drug substances dissolved quite well in molten PEG. Several drugs have been incorporated in PEG, resulting in either eutectic or monotectic mixtures [14,19-23]. The phase diagrams of a typical eutectic mixture and a monotectic mixture (for example, a mixture of PEG and drug) are shown in Fig. 1a-b. Both eutectic and monotectic mixtures are described as systems in which drug and PEG are miscible

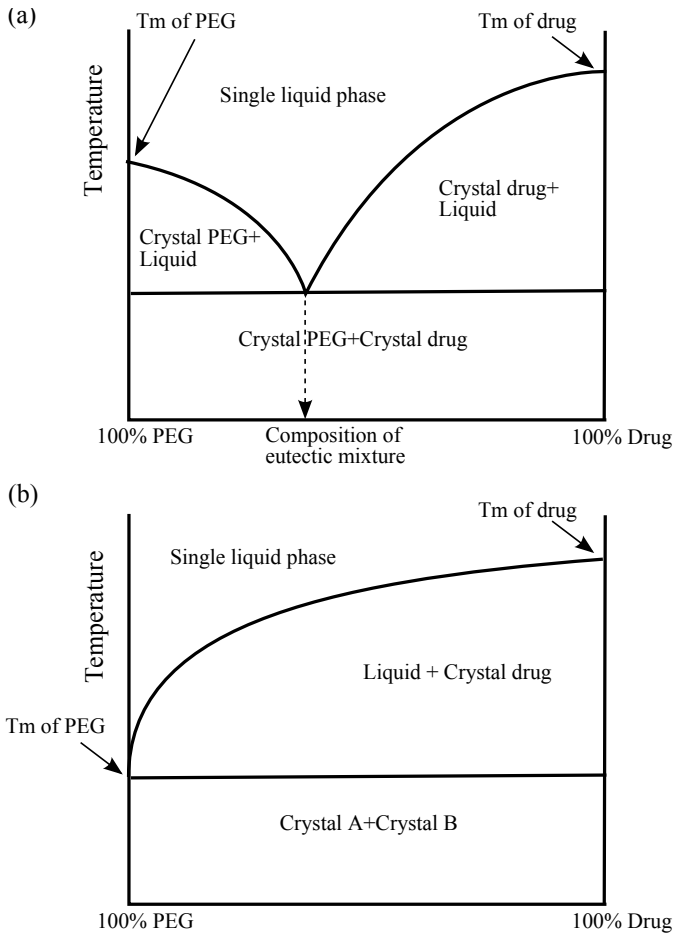

Figure 1 Phase diagrams of typical (**a**) eutectic mixture and (**b**) monotectic mixture (for example, a mixture of PEG and drug).

in liquid state; however, the system is immiscible in the solid state, existing as two crystalline phases of the pure components. The melting point of a eutectic mixture is below that of the pure drug and PEG whereas in the case of monotectic mixture, the melting point of PEG remains constant and is independent of the amount of drug. When a mixture of eutectic composition is cooled, both drug and carrier will crystallize simultaneously which facilitates the formation of small crystals. In contrast, when either drug or carrier starts to crystallize first, the chance to obtain large crystals is high. Therefore, the eutectic mixture is desirable because it yields small drug and carrier crystals resulting in an increased dissolution rate. Furthermore, a lower process temperature than the melting points of drug and carrier can be used for eutectic mixtures. A eutectic mixture of fenofibrate and PEG 8000 is formed at a drug load

of about 20-25% w/w [24]. The particle size of fenofibrate in the eutectic mixture was more than 10 times smaller than that of the unprocessed fenofibrate. In addition, it has been found that when fenofibrate [20] or naproxen [23] was incorporated in PEGs of various molecular weights, the dissolution rate of these drugs was independent on the molecular weight of PEG. It has also been found that these drugs did not interact with PEG. In contrast, it has been found that flurbiprofen did interact with PEGs and that the dissolution rate of solid dispersion of flurbiprofen in PEG increased with decreasing molecular weight of PEG. This result was attributed to the increased extent of interactions and increased solubilizing capacity of the carrier with decreasing molecular weight [20].

Poloxamers are nonionic surfactants composed in of polyoxyethylene–polyoxypropylene-polyoxyethylene triblock copolymers. The two polyoxyethylene parts are hydrophilic whereas the polyoxypropylene part is hydrophobic. Poloxamers have a T_m of 52-57°C. Poloxamer 188 [25-28] and poloxamer 407 [29-31] have been used as carrier for various model drugs. These studies consistently reported that the state of the drugs was partly crystalline and partly amorphous. The observed increased dissolution rate of the drugs is most likely due to the decreased particle size, the reduced crystallinity of the drug, and the surface-active property of poloxamer itself. Shah et al. prepared poloxamer 188-based solid dispersions containing rofecoxib at varying cooling temperatures and drug loads [32]. A decrease in cooling temperature and an increase in amount of poloxamer 188 resulted in an increased dissolution rate of drug, possibly due to higher proportion of amorphous rofecoxib in the solid dispersions. However, some studies found that an increase in the amount of poloxamer led to a decrease in drug dissolution rate because poloxamer at high concentration forms a gel during dissolution [25,29].

Solid dispersions composed of a drug incorporated in a combination of PEG with other additives have also been investigated. The purposes of using additives are to increase miscibility of drug and carrier, to increase the drug load, to enhance the dissolution behavior of solid dispersions, or to improve the storage stability of solid dispersions. An example of such a third component are surfactants [16,33-45]. About less than 3% w/w griseofulvin completely dissolved in molten PEG 6000. Interestingly, when 2% w/w sodium dodecyl sulphate was incorporated in the binary mixtures, griseofulvin could be dissolved in molten PEG 6000 up to a drug load of 40% w/w, indicating that the surfactant increased the miscibility of the components [40]. PEG is a semi-crystalline carrier which contains both crystalline and amorphous components [46]. Wuff et al. and Alden et al. have prepared micelles with lipophilic drugs incorporated and mixed them in molten PEG [39,47]. After cooling, the micelles were incorporated in the amorphous fraction of PEG. Dissolution behavior of ternary dispersions containing drug, PEG and surfactant was significantly improved as compared to the dispersions without surfactant. Also the type and the amount of surfactant incorporated in the dispersions affect the dissolution behavior of drugs

[34,37]. However, increasing the concentration surfactant to 10% w/w in the ternary dispersions did not give the further improved dissolution of glyburide [33].

Polymers as a third component have also been incorporated in binary dispersions. A solid dispersion of nifedipine and PEG 1500 showed excellent dissolution behavior, but was unstable upon storage. Combinations of the drug with PEG 1500 and PVP (K12 and K30), polyvinylpyrrolidone-co-vinylacetate (PVPVA 64) or Eudragit® EPO at a ratio of 1:1 were melted at 140°C allowing the formation of homogeneous mixtures. A superior dissolution behavior of nifedipine after storage was found with the combination of PEG 1500 and PVPVA 64, probably because of the low mobility of drug in PVPVA 64 and consequently a slow re-crystallization upon contact with dissolution medium [48].

2.4.1.2 Hot melt extrusion (HME)

Hot melt extrusion is a combination of melting and a mechanical process in which drug, polymer and optionally plasticizers are mixed and melted under controlled conditions of temperature and shear forces. The mass of co-melts is mixed with the help of the transport screws and extruded through a die plate, yielding solid dispersions. Extensive reviews on hot melt extrusion technology have been published previously [49-51].

The most important parameter for this hot melt extrusion is the process temperature. The optimal process temperature is determined by the T_m of the drug, the T_m of the crystalline carrier, the T_g of the amorphous carrier and the thermoplastic properties of the carrier. During the extruding process, the drug should be thoroughly mixed with the carrier and both should not degrade at the process temperature. In general, the process temperature has to be higher than T_m or T_g of the carrier to soften and thereby decrease the viscosity of the carrier allowing sufficient flow through the extruder. Therefore, the T_m or the T_g of carrier should not be too high to limit the risk of drug degradation and/or to yield a practically process temperature.

Determination of the decomposition temperature of drug, carrier or mixture of drug and carrier are beneficial for setting the maximum process temperature [52]. Thermal gravimetric analysis (TGA) is a useful method only if the substances change in weight during degradation. In addition, to screen the miscibility of the drug in the carrier, estimation of solubility parameters, thermal analysis e.g. by differential scanning calorimetry (DSC) and hot stage microscopy (HSM) are useful techniques [53-55]. Such investigations indicate the most suitable carrier for a specific drug. If the drug is miscible with the carrier, it has the potential to form a glass solution.

Carriers, which have been widely used with this method, can be divided into two categories: synthetic polymeric carriers and carbohydrate carriers. Examples of synthetic polymeric carriers are PVP K30, PVPVA 64 and Eudragit® E100 (polymethacrylates). These polymers are amorphous in nature. In addition, they have the thermoplastic properties which are required for the extrusion process. Solid dispersions have successfully been prepared from these polymers. For example,

tolbutamide, indomethacin, nifedipine or lacidipine have been incorporated in PVP K30 or PVPVA 64 at a drug load of 50% w/w. The extruder temperature was close to the T_ms of drugs. It is concluded that glass solutions of these drugs and carriers can only be obtained if the drugs are completely dissolved in the rubbery/molten carrier and if no phase separation occurs during the process (e.g. during the cooling of the product). Most solid dispersions showed improved dissolution rates as compared to their corresponding physical mixtures. In addition, all these solid dispersions remained stable during storage at 25°C/<10%RH for 8 weeks. However, during storage at 25°C/75%RH, only the solid dispersions of indomethacin incorporated in PVP K30 or PVPVA 64 were stable. The differences in physical stability of the drugs/carriers are possibly due to the differences in degree of hydrogen-bonding between drug and carrier [56]. In another study, fenofibrate was incorporated in PVPVA 64 or Eudragit® E100 at a drug load of 33% w/w. In these cases, no glass solutions were formed. Instead, the drug was incorporated in the carrier partially in the amorphous state and partially in the crystalline state. Dissolution of the solid dispersion with PVPVA 64 as carrier was slower than that with Eudragit® E100 as carrier due to gel formation of PVPVA 64 during dissolution. Interestingly, the bioavailability of Eudragit® E100 solid dispersion was superior to the marketed product fenofibrate capsules [57]. An increased bioavailability of a solid dispersion prepared by hot melt extrusion as compared with the marketed product was also found with a solid dispersion in which nimodipine was incorporated in PVPVA 64 [58].

Examples of carbohydrate carriers that are frequently used in solid dispersions prepared by hot melt extrusion are cyclodextrin (CD) derivatives and HPMC. The dissolution behavior of solid dispersions of ketoprofen incorporated in β-CD or sulfobuthyl ether-β-cyclodextrin (SBE_7βCD) at a drug load of 50% w/w was compared. The drug was incorporated in the carriers predominantly in the crystalline state. Solid dispersion from SBE_7βCD gave a higher dissolution rate than that from β-CD, possibly because the drug interacts stronger with SBE_7βCD than with β-CD during dissolution [59] also the surface active properties of the SBE_7βCD may have played a role. In another study, a solid dispersion of itraconazole and HPMC 2910 at a drug load of 40% was prepared. The drug was amorphous in the carrier resulting in an increased dissolution rate as compared to the corresponding physical mixture. Furthermore, after storage for 6 months at 40°C/75% RH, the solid state of the drug and the drug content in the solid dispersion did not change [60].

Besides the carrier, additives are frequently used in the formulations in order to decrease the T_m or T_g of carriers and/or to facilitate the flow of the mixture through the extruder. This enables a reduction of the process temperature. Surfactants are the most used plasticizers in formulations for hot melt extrusion. They can interact with carriers resulting in increased chain mobility by which the T_m or T_g of carriers are decreased. For example, solid dispersions of a poorly soluble drug (name not specified) and the surfactant Tween® 80 incorporated in PVP K30 or HPMC E5 were investigated. It was

found that the melt viscosity of all mixtures with Tween®80 was lower than that of the corresponding mixtures without the surfactant. Furthermore, fully amorphous solid dispersions were obtained from both carriers [61]. However, probably due to their lowered T_gs, the solid dispersions showed a limited storage stability since the drug partially crystallized in both cases during storage at 30°C/60%RH [62].

In addition to surfactants, other additives such as citric acid [63], methylparaben [64] or even the drug [59] can act as plasticizers. Interestingly, in another study, supercritical carbondioxide (CO_2) was injected in the extrusion zone. It has been reported that the supercritical CO_2 was a temporary plasticizer for PVPVA 64, Eudragit® E100 or ethylcellulose, resulting in a decreased process temperature. In addition, the carriers showed after processing with the supercritical CO_2 a pore-structure, resulting in an increased surface area and therefore an increased dissolution rate [65]. Other solid dispersions [66-77] prepared by hot melt extrusion are summarized in Table 2.

2.4.2 Solvent method

The major advantage of using a solvent for the preparation of solid dispersions is that it increases the capability of a drug to be incorporated in a carrier as a solution or suspension at mild temperatures and thereby avoid thermal degradation. Since this production process involves the application of solvents, various technologies for drying have been investigated.

2.4.2.1 Spray drying

Spray drying has been widely used for producing solid dispersions. The process mainly consists of atomization, drying (by heat) and powder collection. Samples to be spray dried can be a solution or a suspension, which normally contains a drug, a carrier, and sometimes additives. The sample is atomized by feeding it through a nozzle, creating fine droplets. The solvent in these fine droplets is rapidly evaporated by hot air or an inert gas, yielding a dry powder. The final product is usually collected by a cyclone system (Fig. 2). Spray drying is an efficient method to produce solid dispersions due to rapid evaporation of the solvent. The feed rate of the solution, the flow rate of the atomizing air, and the inlet temperature and flow rate of the drying gas are process settings that affect the morphology of the powder, the product yield, physico-chemical characteristics of the product and the amount of residual solvent in the powder. Optimization of the process settings has been investigated in many studies [78-80]. Also a model-based methodology for spray drying process development has been described [81].

Organic solvents or co-solvents are used because of the poor aqueous solubility of many drugs. With a proper choice of solvent or co-solvent system, solutions with a relatively high solid content can be prepared by which an efficient process and a high production output can be achieved. Because the final product will often contain a certain amount of residual solvent(s), the use of toxic solvents should be avoided. Nevertheless, in many studies highly toxic solvents like dichloromethane or chloroform

Table 2 Examples of solid dispersions prepared by hot melt extrusion.

Drug	Carrier	Plasticizer	Remarks	Ref.
Spironolactone	HPβCD	sorbitol, and corn starch	Corn starch was used to improve the thermoplastic property of the mixture. The process temperature could be decreased.	[69]
Itraconazole	HPMC: HPβCD	--	Ratio between the two carriers was optimized to allow an efficient process. The optimized ratio of HPMC: HPβCD was 45:15.	[76]
Itraconazole	Eudragit® L100-55: Carbopol®974P	triethyl citrate	- Amorphous solid dispersion was obtained. - Carbopol®974P was used in formulation to sustain the supersaturation concentration of the drug from Eudragit® L100-55 at neutral pH.	[74]
Bicalutamide	PVP K25	--	At maximum drug load of 30% w/w, glass solutions were obtained. The amorphous solid dispersion was stable for 12 months at 20°C/40%RH.	[66]
Indomethacin	- Eudragit® EPO - PVP K30 - PVPVA 64 - poloxamer 188	--	Eudragit® EPO, PVP K30 or PVPVA 64 were miscible with the drug. In contrast, poloxamer 188 was partially miscible with the drug.	[75]
Indomethacin	- Eudragit® EPO - PVP K30 - PVPVA 64	--	Storage stability for 3 months at 40°C/75%RH, intrinsic dissolution rate of dispersions from Eudragit® EPO was superior to that from the other two carriers.	[73]
Hydrocortisone	- PVPVA 64 - HPMC E3	--	PVPVA 64 allowed a lower process temperature than HPMC E3.	[67]
Ritonavir	PVPVA 64: colloidal silicon dioxide	sorbitan monolaurate	Ritonavir was amorphous in the carrier. Nano/micro particulates were obtained when the solid dispersion was dispersed in an aqueous medium.	[70]
17β-Estradiol hemihydrate	- PEG 6000 - PVP K30 - PVPVA 64	- Sucroester® WE15 - Gelucire® 44/14	Solid dispersions with PVP K30 and Sucroester® WE15 yielded a proper flowability of mixture and the fastest dissolution. The drug in this solid dispersion was partially crystalline.	[77]
Celecoxib	Eudragit® EPO	--	Solid dispersion with a drug load of 50% w/w showed an improved dissolution rate. The solid dispersion was stable during storage for 6 months at 25°C/60%RH.	[71]

Table 2 Examples of solid dispersions prepared by hot melt extrusion (continued).

Drug	Carrier	Plasticizer	Remarks	Ref.
Celecoxib	PVP K30	--	- Introducing the supercritical CO_2 in the process to yielded the solid dispersions with porous structure. - Solid dispersion with a drug load of 30% w/w was a glass solution. Supercritical CO_2 did not affect the solid state of drug in the carrier. The solid dispersion was stable for 3 month at 40°C/75%RH.	[68]
A model drug (blind name)	PVP K30	sorbitol	Firstly, the drug crystalline was converted to an amorphous state. Secondly, the obtained amorphous drug was incorporated in the carrier at 20% w/w drug load by hot melt extrusion process. The solid dispersion showed an increased bioavailability after oral administration as compared to the corresponding physical mixture.	[72]

have been used. Differences in evaporation rate of the solvents and solubility of solutes in the solvent or co-solvent system can influence the particle morphology. Rizi et al. prepared solid dispersions of hydrocortisone in Eudragit® L100 by varying ethanol/water ratios (100/0, 75/25 and 50/50) [82]. Spray drying with pure ethanol gave particles with a wrinkled surface whereas the use of ethanol/water co-solvent mixtures resulted in more spherical particles.

The procedures used to incorporate a drug in a carrier by spray drying can influence the solid state of drug in the final solid dispersion. For example, tacrolimus was incorporated in hydroxypropyl-β-cyclodextrin (HPβCD) and dioctyl sulfosuccinate (DOSS) by three different procedures. In the first procedure, the drug, HPβCD, and DOSS were dissolved in a dichoromethane/ethanol mixture. In the second procedure, the drug and DOSS were dissolved whereas the carrier was dispersed in ethanol. And in the third procedure, HPβCD and DOSS were dissolved while drug was dispersed in water. The two samples in which the drug was dissolved (first and second procedure) yielded solid dispersions with tacrolimus incorporated in the amorphous state. Obviously, the sample in which the drug was dispersed (third procedure) yielded a solid dispersion with tacrolimus incorporated in the crystalline state. The first procedure gave the highest dissolution rate of tacrolimus followed by the second procedure [83]. It is well known that cyclodextrins and lipophilic drugs can form inclusion complexes which readily dissolve. Obviously, such complexes can only be formed when both components are in the dissolved state. Therefore, only during the preparation of the solid dispersion via the first procedure a tacrolimus-HPβCD complex could have been formed. The more rapid dissolution of the solid dispersion prepared via the first procedure compared to that prepared via the second procedure indicates that indeed the complex has been formed. The slowest dissolution rate as found for the solid dispersion prepared via the third procedure can be ascribed to the crystalline nature of the drug and the fact that the crystal size was not decreased.

Nanosuspensions have been prepared by high-pressure homogenization or wet ball milling. These nanosuspensions have been spray dried to render the formulation into a solid dosage form. In general, the nanosuspension consists of nano-sized drug crystals dispersed in an aqueous medium containing surfactants and/or polymers. The surfactants and/or polymers are needed to prevent aggregation of the drug particles and particle growth by Ostwald ripening. In addition, spray drying of a nanosuspension requires excipients for forming hydroplilic matrices, and aiding the spray drying process. Thus, the obtained products can be regarded as solid dispersions. For example, a nanosuspension of the lipophilic drug candesartan cilexetil (10% w/v) in HPMC (2% w/v) and sodium dodecyl sulfate (1% w/v) was prepared after which mannitol (73% w/w with respect to the drug content) was added then spray dried. Because of its low T_g (13°C), mannitol crystallized during spray drying and a fully crystalline solid dispersion was obtained. Furthermore, after reconstitution of the spray dried powder with water, the particle size of drug was comparable to that of

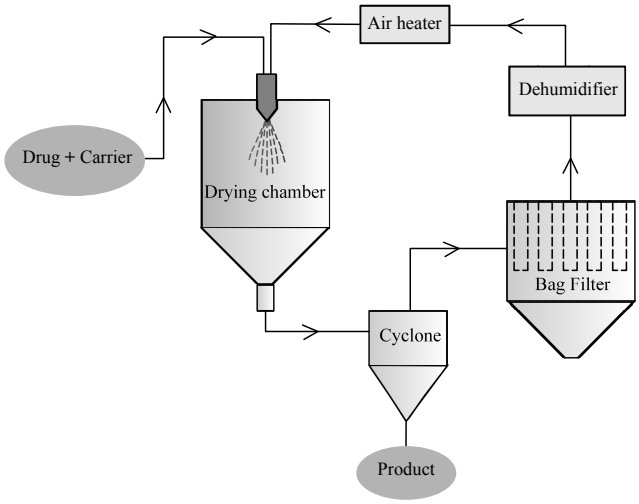

Figure 2 Process flow of spray drying.

the original nanosuspension. In addition, the dissolution rate of the solid dispersion was higher than that of drug microparticles and resulted in a higher bioavailability after oral administration in rats [84]. In another study, itraconazole nanosuspensions dispersed in aqueous solutions of different sugars, i.e. sucrose, dextrose, lactose and mannitol, were spray dried. Spray-dried powder with mannitol as carrier yielded the optimal powder; it was free flowing and had low moisture content probably due to the crystalline nature of mannitol. In contrast, the spray-dried powder with lactose as carrier had a high moisture content probably because lactose was amorphous, however, it was still free flowing. The spray dried powders using sucrose or dextrose as carrier were sticky [85]. Most likely, also these sugars were amorphous and due to their high moisture content, their T_g was below ambient temperatures. Also spray drying of nanosuspensions containing other lipophilic drugs such as fenofibrate [86], celecoxib [87] and cefpodoxime proxetil [88] using various carriers have been studied.

Colloidal silicon dioxide is often added to solutions or dispersions containing drug and carrier to be spray dried [89-92]. The reason is that this material has a very large specific surface area onto which the drug can deposit, by which it is very finely dispersed, resulting in excellent dissolution behavior. A concomitant advantage is that usually a high product yield is obtained and that the product shows improved flow properties.

A highly undesired phenomenon that may occur during spray drying is the formation of a sticky product at the outlet of the spray drier. Due to its stickiness, the product will adhere to the cyclone resulting in a low product yield. Several factors affect whether or not a sticky product is obtained. First, the glass transition temperature

(T_g) of the carrier if it does not crystallize during spray drying. Obviously, it should be higher than the outlet temperature otherwise it will be in the rubbery and thus sticky state. For example, spray drying of carbamazepine with PVPVA 37 or PVPVA 64 has been investigated. These two polymers have different pyrrolidone/vinyl acetate monomer ratios yielding different T_gs. The T_gs of PVPVA 37 and PVPVA 64 are 55°C and 106°C, respectively. The spray-dried product using PVPVA 64 was glassy whereas that using PVPVA 37 was rubbery. This result is caused by the fact that the outlet temperature of 74°C which is higher than the T_g of PVPVA 37 but lower than the T_g of PVPVA 64 [9]. Secondly, a too high residual solvent content of the product can cause the stickiness of product because solvents act as plasticizers reducing the T_g. The solvent can be removed more efficiently by increasing the inlet temperature and thereby accelerating the evaporation rate of the solvent and/or by using a taller drying chamber to allow enough time for solvent evaporation.

2.4.2.2 Freeze drying

Another method to prepare solid dispersions is freeze drying. Freeze drying consists of three successive steps: freezing, primary drying and secondary drying. A sample to be freeze dried typically consists of a drug, excipients, and one or more solvents. During the freezing step, the solutes as well as the solvents are solidified by freezing. To explain what happens during this step, we consider a simplified system consisting of just one solute and one solvent (Fig. 3). Upon cooling, initially only the solvent (e.g. water) crystallizes. Since the solvent crystallizes, the concentration solute in the remaining solution increases. This continues until the eutectic temperature (T_e) is reached, after which the solute also can crystallize by which a eutectic mixture is formed. However, the solute usually crystallizes slower than the solvent. Thus, if the solution is cooled sufficiently fast, the solute does not crystallize, but crystallization of the solvent continues until the glass transition temperature of the maximally freeze-concentrated fraction (T_g') is reached. If the solution is cooled further, the mobility of the molecules is strongly reduced. Due to the reduced mobility neither the solute nor the solvent crystallize further and a rigid glass is formed [93].

During primary drying, the solvent crystals are removed from the sample by sublimation. Thereto the pressure in the freeze dryer is reduced. During primary drying, the product temperature should stay below the T_e (for eutectic mixtures) or T_g' (for glasses) to avoid solvent melting and thereby to avoid the sample to collapse. After sublimation of the solvent crystals, a porous cake is obtained.

During secondary drying, the unfrozen solvent is removed by desorption. Thereto, the shelf temperature is gradually raised, typically to ambient temperature, while the chamber pressure is further decreased. The unfrozen solvent is removed by diffusion through the freeze dried matrix and evaporation at the solid surface. Since amorphous products can absorb relatively large amounts of solvents, secondary drying is usually necessary to obtain a product with a sufficiently low moisture content. In contrast,

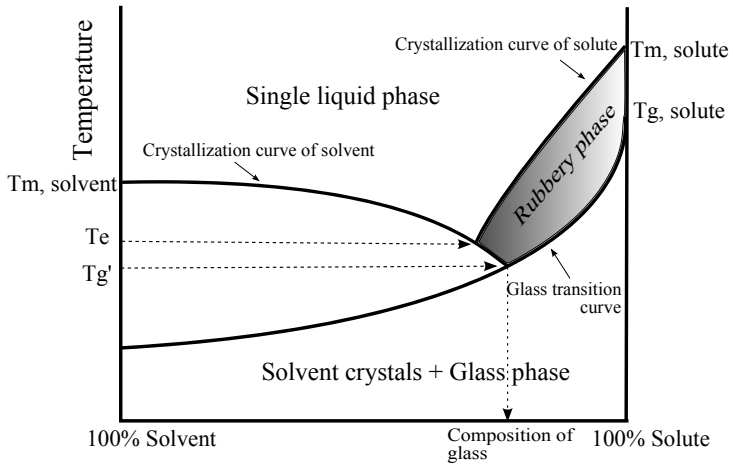

Figure 3 Phase diagram of a binary system during freezing.

crystalline products usually adsorb only small amounts of solvent. Therefore, for crystalline materials, most of the solvents may already have been sublimated during primary drying, and secondary drying is not always necessary.

In the previous paragraphs, the sample composition was simplified to just one solute in a solvent to explain the freeze drying process. However, since the solubility of lipophilic compounds in water is low, usually these compounds are freeze dried from more complex co-solvent systems. Ideal co-solvents for freeze drying should have a high vapor pressure to ensure a high sublimation rate and a high melting point to allow the solvents to be frozen easily. An example of a such a co-solvent is *t*-butyl alcohol (TBA). Its vapor pressure (41.25 mmHg) [94,95] and its melting point (T_m = 25°C) are relatively high [96]. More important than the melting temperature, is the eutectic temperature of a co-solvent system. The water/TBA co-solvent system has relatively high eutectic temperatures of -5°C and -3°C [95]. Therefore, it can be easily frozen at typical freeze drying temperatures. This in contrast to for example a water/ethanol co-solvent system, which has a relatively low eutectic temperature of -124°C [97]. Another advantage of using TBA as co-solvent, is that small needle-shaped solvent crystals are formed upon freezing. After sublimation of these needle-shaped crystals, a dry product layer with little resistance is formed which shortens the drying process [98]. Despite several limitations such as the limited level of residual solvents and the difficulty to handling or storage, co-solvent systems such as ethanol/water [99] and 1,4-dioxane/water [100] are used as well. Other practical aspects of freeze drying using co-solvent systems has been well reviewed by Teagarden and Baker [101].

High freezing rates can be achieved by using cryogenic liquids such as liquid nitrogen. Either vials containing the solution can be immersed in the cryogenic liquid

or the solution is sprayed directly into the cryogenic liquid. By using a nozzle small droplets can be generated, which are then rapidly frozen. Thereafter, the frozen samples are transferred into a freeze dryer to continue with the primary and secondary drying stages. The nozzle position can be underneath [102,103] or above the surface of the cryogenic liquid [12]. The advantage of solid dispersions prepared by spray-freezing into a cryogenic liquid is the formation of very small porous particles. Therefore, the surface area of these solid dispersions is strongly increased. For example, solid dispersions containing danazol and HPβCD prepared by spray-freezing into liquid nitrogen had a surface area of 113.5 m^2/g, while the solid dispersion prepared without the spray-freezing technique had a surface area of only 0.16 m^2/g. Consequently, the dissolution rate of the drug from the solid dispersion prepared by using spray-freezing was faster than when the solid dispersion was prepared by freezing the bulk solution [102]. In addition, the type of solid dispersion that is formed can be influenced by the freezing method. For example, a water/TBA solution containing diazepam and inulin 4 kDa was frozen by two different methods: immersing a vial containing the solution in liquid nitrogen and spraying the solution into liquid nitrogen. A glass solution was obtained from spray-freezing whereas a glass suspension was obtained when the vial was frozen in liquid nitrogen [12].

A freezing method that is suitable for large scale production, is spraying the solution on the surface of a solid cold substrate. Purvis et al. sprayed a solution of the lipophilic drug repaglinide in a 1,4-dioxane/TBA/water co-solvent system on such a cold substrate. The frozen droplets were collected and then freeze dried. This resulted in amorphous dry particles that consisted of porous nanostructured aggregates. Dissolution of the drug from this amorphous solid dispersion was higher than that of the unprocessed drug [104]. Another technique that can be used for large scale production of solid dispersions is spray-freeze drying by using a three-way nozzle [105]. Since a matrix/water solution and a drug/organic solvent solution flow separately through this nozzle, highly concentrated solutions can be spray-freeze dried without the risk of unwanted recrystallization of one of the solutes from the solution before it is frozen. Therefore, relatively large amounts solid dispersion per batch can be produced.

Although the principle to obtain a solid dispersion is different, also by freeze drying nanosuspensions, crystalline solid dispersions can be obtained [106-108]. Van Eerdenbrugh et al. for example, freeze dried nanosuspensions containing nine different model drugs and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as a stabilizer [106]. These solid dispersions showed the tendency to agglomerate, resulting in a lower dissolution rate. However, when excipients such as sucrose [107] or a surfactant [109] were added to the nanosuspension before drying, powder agglomeration could be prevented.

2.4.2.3 Supercritical fluid drying

Another method to prepare solid dispersions of poorly water-soluble drugs is supercritical fluid drying. A supercritical fluid is a fluid that is pressurized above its

critical pressure (P_c) and heated above its critical temperature (T_c). A supercritical fluid exists as a single fluid phase with physicochemical behavior in between a liquid and a gas. The liquid-like characteristics are beneficial for dissolving the solute while the gas-like characteristics are advantageous for rapid precipitation of solutes. Carbondioxide (CO_2) is commonly used for supercritical fluid drying, because it is non-toxic, non-flammable, cheap, recyclable after processing, and environmentally friendly. Furthermore, due to the relatively low critical point of CO_2 (74 bar and 31°C), it allows for easy processing, which makes it suitable for pharmaceutical products [110].

Supercritical fluid drying can be separated into two categories: firstly, the supercritical fluid can be used as a solvent or secondly, the supercritical fluid can be used as an antisolvent [111]. When the supercritical fluid is used as solvent, the drug is dissolved in the supercritical fluid and subsequently this supercritical solution is sprayed through a nozzle into an expansion chamber in which the pressure and/or the temperature are decreased. Due to the decreased pressure and/or temperature, the solubility of drug in supercritical fluid decreases, leading to precipitation of the drug. This process is known as rapid expansion of supercritical solutions (RESS) [112]. Initially, this method was used for precipitating pure drugs [113,114]. However, supercritical CO_2 has also been used to prepare solid dispersion, e.g. a solid dispersion of piroxicam incorporated in β-cyclodextrin [115]. The main disadvantage of using supercritical CO_2 as solvent to prepare solid dispersions is that both the drug and the hydrophilic carrier have to be soluble in supercritical CO_2 which is for many drug/carrier combinations not the case.

When the supercritical fluid is used as an antisolvent, first a solution of the drug and a carrier is prepared. This solution is then saturated with supercritical CO_2, resulting in a decreased solubility of the drug and the carrier in the organic solvent and consequently in precipitation of the drug and the carrier. Two requisites of this method are i) drug and carrier should be soluble in the organic solvent but not soluble in the mixture of supercritical CO_2-organic solvent and ii) the organic solvent should be miscible with supercritical CO_2. Under the supercritical fluid as an antisolvent, different ways to introduce a solution of sample and supercritical CO_2 into a precipitating chamber which have been used are gas antisolvent precipitation (GAS), precipitates by compressed antisolvent (PCA), supercritical antisolvent (SAS), aerosol solvent extraction system (ASES) and solution enhanced dispersion by supercritical fluids (SEDS) [116].

Effects of drug load and the concentration of drug and carrier in the solution on the solid state were studied by Kluge et al. Phenytoin was incorporated in PVP K30 at different drug loads. The drug in solid dispersion with drug loads below 40% w/w was amorphous, whereas at a drug load higher than 40% w/w the drug was partially amorphous and partially crystalline. Furthermore, it was found that a change in total concentrations of phenytoin and PVP K30 in the starting solution did not affect the crystllinity of the drug in carrier [117].

Other factors such as the type of carrier and type of organic solvent can influence the characteristics of solid dispersions and the product yield. For example, oxeglitazar at a drug load of 50% w/w was incorporated in different carriers: PEG 8000, poloxamer 407 and PVP K17. Solid dispersions with PEG 8000 and poloxamer 407 yielded needle-like drug crystals, partially covered with the carriers. Solid dispersion with PVP K17 on the other hand, resulted in irregular shaped particles with a lower degree of crystallinity. Furthermore, a higher amount of residual solvent was found with PVP K17 as carrier than when the other carriers were used. In the same study, different organic solvents (ethanol, dichloromethane and chloroform) were evaluated. When dichloromethane and chloroform were used, a higher product yield was obtained than when ethanol was used. Nevertheless, the use of chloroform resulted in the lower amount of drug which can be incorporated in the carriers as compared to the theoretical value. Overall, PEG 8000 and poloxamer 407 as carriers and dichloromethane as solvent resulted in the highest product yield, lowest residual solvent content and the highest efficiency of drug incorporation. However, poloxamer 407 yielded the higher polymorphic purity of drug in the carrier than PEG 8000. Therefore, the optimum carrier and solvent for this study were poloxamer 407 and dichloromethane, respectively. In addition, these solid dispersions showed improved dissolution behavior of oxeglitazar than when a physical mixture was used [118]. Other solid dispersions [119-130] prepared by using supercritical fluid as an antisolvent are summarized in Table 3.

2.5 EXPERT OPINION

The application of solid dispersions has successfully improved the bioavailability of lipophilic drugs. In this review, the most commonly applied methods to prepare solid dispersions and formulation considerations are described. The advantages and disadvantages of the described methods are summarized in Table 4. Many studies have proven that solid dispersions prepared by these methods can increase the dissolution rate of several lipophilic drugs and thereby their bioavailability. Other critical aspects related to solid dispersions are that they should be stable upon storage and that they can be produced at large scale.

The fusion method is the easiest method to prepare solid dispersions. Since it is a fast process, this method is useful to screen formulations. However, due to the difficulty to control the temperature during preparation, phase separation between drug and carrier can easily occur. Since this phase separation can not be controlled well, it may result in the formation of large drug particles which obviously will dissolve slowly. In addition, when amorphous drug particles are formed, undesired crystallization during storage can occur. Therefore, due to the poor temperature control, the fusion method is considered less suitable for large scale production.

Hot melt extrusion is a similar method as the fusion method because in both methods the drug and carrier are first heated and subsequently cooled to obtain the

Table 3 Examples of solid dispersions prepared by supercritical CO_2 as antisolvent.

Drug	Carrier	Solvent	Remarks	Ref.
Nifedipine	PEG 4000	--	Supercritical CO_2 was dissolved in melts of drug-PEG instead of using a solvent. Drug dissolution improved. Drug load not described.	[130]
Carbamazepine	PEG 4000	acetone	Drug was crystalline (8.3% w/w drug load). Drug dissolution was improved.	[129]
Carbamazepine	- PEG 8000 - PEG 8000: Gelucire® 44/14 - PEG 8000: TPGS	methanol	- Drug was crystalline in all solid dispersions (16.7% w/w drug load). - Dissolution rate was increased in the order: PEG < PEG +Gelucire® < PEG + TPGS.	[128]
Carbamazepine	- PVP K30 - PVP K30: Gelucire® 44/14 - PVP K30: TPGS	methanol	- Drug was amorphous in all solid dispersions (16.7% w/w drug load). - Intrinsic dissolution rate was increased in the order: PVP+Gelucire® < PVP+ TPGS < PVP.	[126]
Piroxicam	PVP K25	dichloromethane	Fully amorphous solid dispersion (20% w/w drug load) was obtained. Dissolution of drug was improved.	[121]
Indomethacin	PVP K90	dichloromethane: acetone (20:80)	- Fully amorphous solid dispersions were obtained with drug loads up to 50% w/w. - The solid dispersion (50% w/w drug load) remained stable for 7 months at 75% RH and room temperature.	[119]
Itraconazole	hydroxypropyl-β-cyclodextrin	dichloromethane: ethanol (30:70)	Complexes with a maximum molar ratio of 1:2 (drug:carrier) were formed. The dissolution rate of the drug was improved.	[122]
Itraconazole	HPMC 2910	dichloromethane: Ethanol (60:40)	- The drug was amorphous in the solid dispersion (60% w/w drug load). - The pharamacokinetics of the drug from the solid dispersion in rats was similar as the marketed product.	[125]
Felodipine	- HPMC 2910 - HPMC 2910: HCO-60 - HPMC 2910:HCO-60: poloxamer 188 - HPMC 2910: HCO-60: poloxamer 407	dichloromethane: ethanol (45:55)	- The drug was amorphous in all solid dispersions (about 10% w/w drug load). - The dissolution rate of the drug from the solid dispersions was increased in the order: HPMC < HPMC 2910: HCO-60: poloxamer 188 < HPMC 2910: HCO-60 < HPMC 2910: HCO-60: poloxamer 407.	[123]

Table 3 Examples of solid dispersions prepared by supercritical CO_2 as antisolvent (continued).

Drug	Carrier	Solvent	Remarks	Ref.
Cilostazol	- poloxamer - TPGS - Gelucire®	dichloromethane	Surfactants (1%) were added to the drug solution. The particle size of the drug was decreased in the order: Gelucire® > drug without surfactant > TPGS > poloxamer.	[120]
Cefuroxime axetil	- PVP K30 - HPMC 2910	dichloromethane: ethanol (60:40)	- Solid dispersions (40% w/w drug load) prepared from PVP and HPMC were fully amorphous. - Dissolution rate of drug was increased for both carriers.	[124]
A model drug (blind name)	- mannitol - Eudragit® E100	- dimethyl sulfoxide: methanol (20:80) for mannitol - dimethyl sulfoxide: acetone (30:70) for Eudragit® E100	- Using Eudragit® E100 yielded fully amorphous solid dispersion (20% w/w) whereas using mannitol did not.	[127]

TPGS = D-α-tocopherol polyethylene glycol 1000 succinate
HCO-60 = polyoxyethylene (60) hydrogenated castor oil

solid dispersion. However, hot melt extrusion is more robust than the fusion method as it is a method by which the drug can be well mixed with the carrier at a controlled temperature leading to a homogeneous and therefore stable and reproducible product. Recently, a solid dispersion was successfully prepared at large scale by hot melt extrusion. This indicates that hot melt extrusion is a viable method and potentially more products prepared by this technique can reach the pharmaceutical market. This explains a recent trend in literature that describes methods to investigate the choice of carriers for specific drugs. Several synthetic polymeric carriers are available for this method. The main disadvantage of hot melt extrusion is that it is limited to thermally stable drugs and to carriers with thermoplastic properties.

Spray drying and freeze drying are methods to produce solid dispersions that have been used for many years. The influence of process parameters on the product properties has been extensively studied. Spray drying can be performed as a continuous process and is therefore suitable for large scale production. Freeze drying is a batch process but can also be used for large scale production although it is expensive and time consuming. Therefore, the research trends that can be found in recent literature are process modifications to increase the versatility of these methods For example, spray drying at low temperature that can be applied to carriers with a low melting point or glass transition temperature. Another example is the adjustment of the freeze drying process into a spray freeze drying process. The main advantage of this adjustment is that the freezing rate is high and can be controlled well. Another interesting development

Table 4 Advantages and disadvantages of fusion, hot melt extrusion, spray drying, freeze drying and supercritical fluid drying.

Methods	Advantages	Disadvantages
Fusion	- Short time process - Solvent free	- Not suitable for thermally labile drugs
Hot melt extrusion	- Solvent free - Good controlled temperature system - Large scale production available	- Not suitable for thermally labile drugs - Carriers without proper thermoplastic properties cannot be used.
Spray drying	- Short time process Micro- to nano-particulates obtained - Robust process - Large scale production available	- Possible solvent residue in the product
Freeze drying	- Robust process - Large scale production available - Mild production condition	- Possible solvent residue in the product - Time consuming - High cost
Supercritical fluid drying (as anitsolvent)	- Mild production condition	- Possible solvent residue in the product - Solubilizing power of supercritical fluid (CO_2) limited

is spray drying or freeze drying of nanosuspensions of drugs. It is well known that nanosuspensions often have an improved bioavailability compared to larger drug forms. Nevertheless, it is a liquid and often not stable dosage form. In general, solid and more stable dosage forms are preferred, therefore, the transformation of nanosuspensions into a dry powder form seems interesting. A dry powder can be filled into capsules or processed into tablets. Although, spray drying and freeze drying are promising methods to prepare solid dispersion, the presence of residual (toxic) solvents in the final product remains a concern as are different aspects of scale up of these processes.

The most recently used method to prepare solid dispersions is supercritical fluid drying. So far, supercritical CO_2 is the most commonly used supercritical fluid in processes where the supercritical fluid acts as antisolvent. Since this process requires that the supercritical fluid and the organic solvents are miscible, the number of suitable solvents is limited. Most studies have used ethanol and/or dichloromethane. Fortunately, many different types of carriers can be used with this process. Many studies have shown promising results. However, extensive investigation of process parameters is required, because these parameters usually determine the properties of the solid dispersions and the product yield. Since large scale production of pure drugs by this method has successfully been performed, we don not expect major technical difficulties with large scale production of solid dispersions by this method.

An important issue is the physical stability of solid dispersions. In general, the solid state of the drug incorporated in carriers can be amorphous, crystalline, or a combination of both. Amorphous solid dispersions are thermodynamically less stable than crystalline solid dispersions. Although many studies have shown that amorphous solid dispersions prepared by the described methods are stable in short-term stability studies, long-term stability is still challenging. Therefore, the interest in the preparation of crystalline solid dispersions is growing. Furthermore, a better understanding of the effects of process conditions and type of drug and carrier on the properties of the final product is required. This will be facilitated by the growing number of *in-line* analytical instruments that are available to investigate phenomena occurring during the production processes.

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CHAPTER 3

EFFECT OF DRUG-CARRIER INTERACTION ON THE DISSOLUTION BEHAVIOR OF SOLID DISPERSION TABLETS

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3.1 ABSTRACT

The objective of this study was to compare the dissolution behavior of tablets prepared from solid dispersions with and without drug-carrier interactions. Diazepam and nifedipine were used as model drugs. Two types of carriers were used; polyvinylpyrrolidone (PVP K12, K30 and K60) and saccharides (inulin 1.8 kDa, 4 kDa and 6.5 kDa). Solid dispersions with various drug loads were prepared by lyophilization. It was found that the drug solubility in aqueous PVP solutions was significantly increased indicating the presence of drug-carrier interaction while the drug solubility was not affected by the saccharides indicating absence of drug-carrier interaction. X-ray powder diffraction and modulated differential scanning calorimetry revealed that all solid dispersions were fully amorphous. Dissolution behavior of solid dispersion tablets based on either the PVPs or saccharides was governed by both dissolution of the carrier and drug load. It was shown that a fast drug dissolution of solid dispersions with a high drug load could be obtained with carrier that showed interaction with the drug.

3.2 INTRODUCTION

Amorphous solid dispersions can be used to improve dissolution rate of poorly soluble drugs [1]. In general, a solid dispersion consists of a hydrophilic carrier in which the drug is dispersed molecularly or as very small particles [2,3]. The mechanisms by which the dissolution rate of the drug is increased are (i) reduction of particle size of the drug, results in a larger surface area available for dissolution and an increased solubility according to the Kelvin equation [2,4,5] (ii) improved wetting properties of the drug [6] and (iii) the higher energy state of the amorphous form compared to the crystalline form gives a higher solubility of drug [7].

In a previous study, we prepared fully amorphous solid dispersions using various saccharides (inulin 1.8 kDa and 4 kDa, and trehalose) as hydrophilic carriers and diazepam as a model drug. Dissolution behavior of tablets prepared from these solid dispersions was evaluated by determining the dissolution rate of the saccharides as well as the drug. A fast dissolution of drug from these tablets occurred when the dissolution profiles of drug and saccharide coincided. However when the drug load was high and/or when the saccharide dissolved fast (e.g. trehalose), the dissolution rate of the drug was slow. This phenomenon was attributed to an uncontrolled crystallization of the drug in the near vicinity of the dissolving tablet due to a high supersaturation [8]. This uncontrolled crystallization resulted in the formation of large crystals which obviously dissolved slowly. Furthermore, it was found that the drug and the carrier in the solid dispersions did not interact. It can be hypothesized that a drug-carrier interaction may affect this undesired crystallization behavior. Therefore, the aim of this study was to investigate the dissolution behavior of tablets prepared from solid dispersions in which drug and carrier do interact and to compare that with the dissolution behavior of tablets prepared from solid dispersions that lack such an interaction. Because it is well known that polyvinylpyrrolidone (PVP) can interact with many lipophilic drugs [9-11]. PVP of various molecular weights was selected in this study as carrier next to the saccharides. Diazepam and nifedipine were used as model drugs.

3.3 MATERIALS

The following materials were used as supplied: diazepam (BUFA B.V. Uitgeest, The Netherlands), nifedipine (Bayer AG, Werk Leverkusen, Germany), polyvinylpyrrolidone (PVP) with different molecular weights: PVP K12 (Acros Organics, Geel, Belgium), PVP K30 (BUFA B.V. Uitgeest, The Netherlands) and PVP K60 (Sigma-Aldrich Chemie, Steinheim, Germany), inulin with various molecular weights: 1.8 kDa, 4 kDa and 6.5 kDa (Sensus, Roosendaal, The Netherlands). Since nifedipine is a photosensitive drug, it was protected from light during all tests.

3.4 METHODS

3.4.1 Determination of solubility

Solubilities of both diazepam and nifedipine in demineralized water, in 10% w/v PVP solutions and in 5% w/v saccharide solutions were determined except for inulin 6.5 kDa because its solubility was very low. All solutions were supplemented with 0.01% w/v benzalkonium chloride to prevent bacterial growth. Samples of diazepam or nifedipine in demineralized water without 0.01% w/v benzalkonium chloride were used as controls. An excess amount of diazepam or nifedipine was added to demineralized water, PVP solutions and saccharide solutions. These suspensions of diazepam or nifedipine in closed vessels were stirred at 37°C for at least 1 week and were then filtered with a 0.2 µm filter prior to analysis. The filtrate was diluted, if necessary, and analyzed by UV-spectrophotometry at wavelength of 230 nm for diazepam or 237 nm for nifedipine. All measurements were performed in duplicate.

3.4.2 Determination of PVP

The concentration of PVP in aqueous solutions was determined as follows: 1.0 mL of a sample was mixed with 2.6 mL of demineralized water and 0.72 mL of reagent. The reagent was prepared by dissolving 31.84 mg I_2, 180.2 mg KI and 2.29 g $ZnSO_4$ in 50 mL of demineralized water. Iodine-PVP complex was analyzed using a UV/VIS-spectrophotometer at a wavelength of 432 nm.

3.4.3 Preparation of solid dispersions (SD)

The PVP-based solid dispersions were prepared as follows: PVP (K12, K30 and K60) and the drug (diazepam or nifedipine) were dissolved in tertiary-butyl alcohol (TBA). The obtained solutions were pipetted into a 20-mL vial (4 mL in each vial). Subsequently, the solution was frozen in liquid nitrogen and lyophilized.

The saccharide-based solid dispersions were prepared as described before [12]. Briefly, the saccharide (inulin 1.8 kDa, 4 kDa and 6.5 kDa) was dissolved in water and the drug (diazepam or nifedipine) was dissolved in TBA. The solutions were mixed at a TBA/water ratio of 4/6 (v/v) (1.6 mL TBA solution and 2.4 mL aqueous solution) in a 20-mL vial. Immediately after mixing, the inulin-diazepam solution was frozen in liquid nitrogen and lyophilized. To produce the solid dispersions with various drug loads the concentrations of drug and carrier were suitably adjusted (Table 1).

In a typical lyophilization cycle the frozen solution was placed on the shelf of a Christ model Alpha 2-4 lyophilizer (Salm and Kipp, Breukelen, The Netherlands). Lyophilization was performed according to a two-step procedure. First, the pressure was set at 0.220 mbar and the shelf temperature at -35°C for one day. Subsequently, the pressure was reduced to 0.05 mbar, while the shelf temperature was gradually raised to 20°C. This condition was maintained for another day. During the whole cycle the condenser temperature was -85°C. After freeze drying the samples were placed in a

vacuum desiccator over silica gel at room temperature for at least one day. An overview of the prepared solid dispersions is given in Table 2.

3.4.4 Preparation of physical mixtures (PM)

Physical mixtures composed of crystalline drugs (as received) and lyophilized carriers in the corresponding ratios of solid dispersions were prepared by gently mixing using a mortar and a spatula. The samples were placed in a vacuum desiccator over silica gel at room temperature for at least one day before use.

Table 1 Composition of solutions for preparation of solid dispersions.

PVP-based solid dispersions		
PVP in TBA (mg/mL)	**Drug in TBA (mg/mL)**	**Drug load (% w/w)**
80.0	4.2	5
80.0	8.9	10
80.0	20.0	20
46.7	20.0	30
Inulin-based solid dispersions		
Inulin in water/TBA (mg/mL)	**Drug in water/TBA (mg/mL)**	**Drug load (% w/w)**
90.0	4.7	5
90.0	10.0	10
22.5[a]	2.5[a]	10
40.0	10.0	20
23.3	10.0	30

[a] Only in case of inulin 6.5 kDa as carrier.

Table 2 Overview of PVP- or inulin-based solid dispersions with various drug loads and tablet compositions.

Carriers	**Drug load diazepam (% w/w)**				**Drug load nifedipine (% w/w)**		
PVP K12	5	10	20	-	5	10	20
PVP K30	-	-	20	30	-	-	20
PVP K60	-	-	20	-	-	-	-
Inulin 1.8 kDa	-	10	20	-	5	10	-
Inulin 4 kDa	-	10	20	30	5	10	-
Inulin 6.5 kDa	-	10	-	-	-	-	-
Compositions of the tablets drug/carrier (mg/mg)	5/95	10/90	20/80	30/70	5/95	10/90	20/80

3.4.5 Tableting

The die of the tableting machine (Hydro Mooi, Appingedam, The Netherlands) was filled with 100 mg solid dispersion or physical mixture without other excipients. The samples were compressed to round and flat tablets using an ESH compaction apparatus equipped with a punch-die set with a diameter of 9 mm. The maximum force of 5 kN was reached in 1 s. The compositions of tablets are shown in Table 2. The tablets had a crushing strength more than 70 N and a friability less than 1% (data not shown). The tablets were stored for at least one day in a vacuum desiccator over silica gel at room temperature before analysis.

3.4.6 X-ray powder diffraction (XRPD)

Samples were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, The Netherlands) with a copper anode (Cu Kα radiation, λ= 0.15405 nm, 40 kV, 40 mA). The diffraction pattern was measured with a step size of 0.008° and a dwell time of 45 s at each step between 4 and 50 2θ at ambient temperature.

3.4.7 Differential scanning calorimetry (DSC)

A modulated differential scanning calorimeter (DSC2920, TA Instruments, Ghent, Belgium) was used to measure glass transition temperature (T_g) of the solid dispersions. About 2-5 mg of sample was weighed in a standard open aluminium pan. An empty pan of the same type was used as a reference. Samples were heated from 25-200°C at a heating rate of 2°C/min, a modulation amplitude of 0.318°C and a modulation period of 60 s. (modulated differential scanning calorimetry (MDSC)) while being purged with pure nitrogen gas. Calibrations of temperature and heat flow were carried out with indium. The inflection point of the transition was taken as the T_g. Furthermore, samples were run at a heating rate of 20°C/min without modulation to measure the degree of relative crystallinity of the drug in solid dispersions (DSC). All measurements were conducted at least in duplicate.

3.4.8 Dissolution experiments

Dissolution of samples was performed by using a USP dissolution apparatus II (Rowa Techniek, Leiderdorp, The Netherlands) with a paddle at 100 rpm and 37°C. The dissolution medium was continuously circulated through UV-spectrophotometer flow cells (Model Ultraspec III; Pharmacia LKB, Uppsala, Sweden) at 20 mL/min using a peristaltic pump (Ismatec, Zurich, Switzerland). The samples were filtered through 0.35 μm filters prior to analysis. Concentrations of diazepam or nifedipine in the dissolution medium were measured every 2 min over a two-hour period at a wavelength of 230 nm for diazepam and 237 nm for nifedipine. Demineralized water (1000 mL) was used as dissolution medium. In a number of cases when PVP based-solid dispersions or PVP based-physical mixtures were evaluated, 1.0 mL samples were taken at different time intervals. Subsequently, the concentration of PVP was determined using the assay as described in Section 3.4.2. Measurements were performed in triplicate.

3.5 RESULTS

3.5.1 Solubility studies

As can be seen in Table 3, the solubility of diazepam or nifedipine in demineralized water with or without benzalkonium chloride added was not significantly different. This indicates that benzalkonium chloride in the applied concentration of 0.01% w/v did not affect the aqueous solubility of the drug. The saturation concentration of diazepam and nifedipine in demineralized water was 63.0 ±1.7 mg/L and 9.0 ± 0.2 mg/L, respectively. These values are in agreement with literature [8,13]. Compared to the solubility of diazepam or nifedipine in demineralized water, the solubility of the drugs in the PVP solutions was strongly increased. The increased solubility in PVP solutions was about 1-3 times for diazepam and was about 4-11 times for nifedipine. Also other studies have found that the solubilities of different model drugs increased in PVP solutions [14-16]. An increasing solubility of nifedipine in the presence of PVP can be ascribed to interactions between the drug and PVP [17]. The increased solubility of diazepam in the different PVP solutions also clearly indicates that this drug interacts with these carriers.

The solubility of diazepam and nifedipine in 5% w/v saccharide solutions (inulin 1.8 kDa and inulin 4 kDa) were similar to those in water (Table 3). This shows that both drugs do not interact with the inulin in aqueous solution. As the aqueous solubility of inulin 6.5 kDa is very low, the dissolving of inulin 6.5 kDa at high concentration (5%

Table 3 Solubility of diazepam and nifedipine in demineralized water, demineralized water with 0.01% w/v benzalkonium chloride, 10% w/v PVP with 0.01% w/v benzalkonium chloride solutions and 5% w/v inulin with 0.01% w/v benzalkonium chloride solutions at 37°C (n=3, mean ± s.d.).

Solutions		**Solubility (mg/L)**	
		Diazepam	**Nifedipine**
Without benzalkonium chloride			
	Demineralized water	63.0 ± 1.7	9.0 ± 0.2
With benzalkonium chloride			
	Demineralized water	58.6 ± 0.7	10.6 ± 0.5
	PVP K12	199.3 ± 6.7	88.9 ± 8.6
	PVP K30	144.1 ± 3.6	105.4 ± 5.2
	PVP K60	89.7 ± 4.2	43.1 ± 0.5
	Inulin 1.8 kDa	59.9 ± 0.3	12.6 ± 0.0
	Inulin 4 kDa	54.7 ± 0.9	11.4 ± 0.4
	Inulin 6.5 kDa	N/A[a]	N/A[a]

[a] The solubility test cannot be conducted because the aqueous solubility of inulin 6.5 kDa is very low.

w/v) in demineralized water could not be prepared. Therefore, the solubility of the drugs in inulin 6.5 kDa (5% w/v) was not available.

3.5.2 XRPD studies

XRPD patterns of all PVP-based solid dispersions with diazepam incorporated showed no distinctive peaks of crystalline diazepam. For example, Fig. 1a shows the XRPD patterns of diazepam, PVP K12, solid dispersion of 20% w/w diazepam in PVP K12 and the corresponding physical mixture. Diazepam as received exhibited the XRPD pattern with sharp peaks which are consistent with literature [18]. PVP K12 presented a broad diffraction pattern indicating its amorphous state. As expected, the physical mixture showed the typical sharp peaks of crystalline diazepam. Compared to the corresponding physical mixture, the solid dispersion showed a broad diffraction peak and lack of the typical sharp peaks of crystalline diazepam. This clearly indicated that 20% w/w diazepam incorporated in PVP K12 was fully amorphous.

Also all PVP-based solid dispersions with nifedipine incorporated was fully amorphous. The XRPD patterns of nifedipine, solid dispersion of 20% w/w nifedipine in PVP K30 and the corresponding physical mixture are shown in Fig. 1b. Nifedipine as received showed the same diffraction pattern as described earlier [19]. The physical mixture of 20% w/w nifedipine in PVP K30 presented the typical sharp peaks of crystalline nifedipine. On the other hand, the corresponding solid dispersion showed a lack of the typical sharp peaks of crystalline nifedipine indicating fully amorphous.

In the case of inulin as carrier, XRPD patterns of all solid dispersions in which diazepam or nifedipine incorporated confirmed that the drugs were fully amorphous. As can be seen in Fig. 1c, for instance, solid dispersion of 10% w/w nifedipine in inulin 4 kDa did not show the typical peaks of crystalline nifedipine.

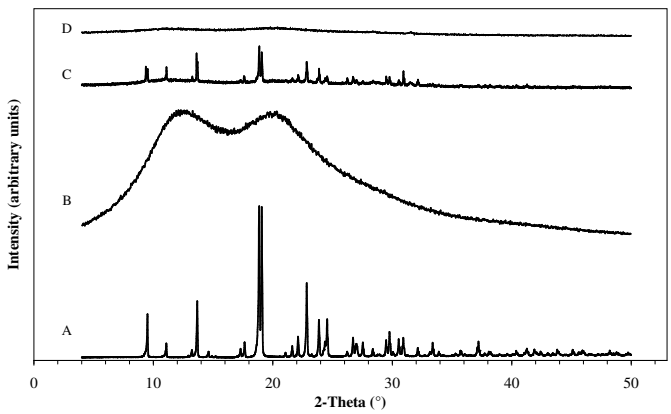

Figure 1a XRPD patterns of (A) diazepam, (B) PVP K12, (C) physical mixture of 20% w/w diazepam in PVP K12 and (D) solid dispersion of 20% w/w diazepam in PVP K12.

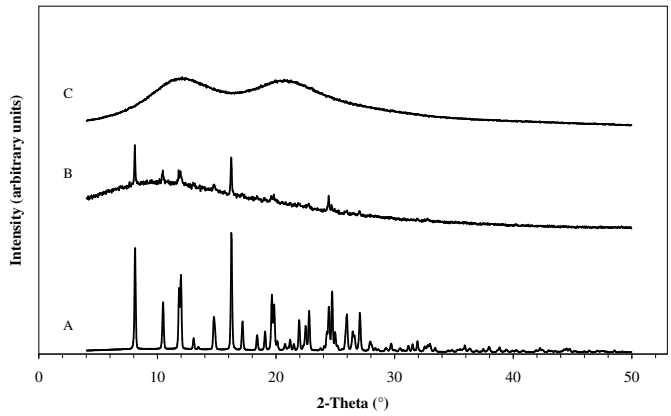

Figure 1b XRPD patterns of (A) nifedipine, (B) physical mixture of 20% w/w nifedipine in PVP K30 and (C) solid dispersions of 20% w/w nifedipine in PVP K30.

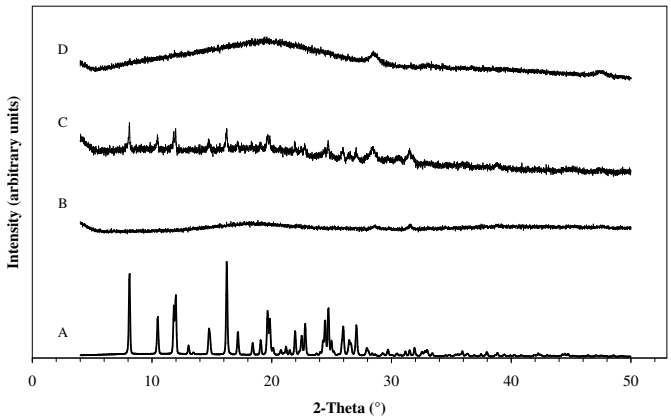

Figure 1c XRPD patterns of (A) nifedipine, (B) inulin 4 kDa, (C) physical mixture of 10% w/w nifedipine in inulin 4 kDa and (D) solid dispersion of 10% w/w nifedipine in inulin 4 kDa.

3.5.3 DSC studies

To investigate whether the drugs were incorporated in the solid dispersions molecularly, as amorphous particles or as crystalline particles, all samples including drugs, carriers, solid dispersions and corresponding physical mixtures were evaluated by (M)DSC.

The melting points (T_m) of diazepam and nifedipine were 131.2°C and 174.0°C, respectively. The T_gs of PVP K12, K30 and K60 were 108.3°C, 173°C and 176.4°C, respectively. Furthermore, T_gs of inulin 1.8 kDa, 4 kDa and 6.5 kDa were 133.1°C, 155.6°C and 179.3°C, respectively.

Except for some carrier/drug combinations as described below, all physical mixtures of PVPs or inulins, and crystalline diazepam or nifedipine at various drug loads showed the $T_g s$ of the carriers and the melting peaks of the drugs corresponding to the pure components. Exceptions were physical mixtures of crystalline nifedipine and PVPs. Thermograms of these physical mixtures showed broad melting peak of nifedipine and shifted to the lower temperature indicating the partial miscibility of drug in carrier during DSC scan. Similar events occurred with a physical mixture of diazepam and PVP K12 (data not presented). Consequently, the corresponding solid dispersions of these carrier/drug combinations were not analyzed by DSC.

All other corresponding solid dispersions did not show the melting peak of either diazepam or nifedipine, indicating that they were all fully amorphous. For instance, as shown in Fig. 2, the solid dispersion with diazepam incorporated at a drug load of 20% w/w in PVP K30 showed one single T_g at 127.5°C indicating that diazepam was molecularly dispersed in these solid dispersions. This was further confirmed by the fact that the T_g was detected at a temperature in between the T_g of pure diazepam 46.2°C and the T_g of PVP K30 (173°C) as predicted by the Gordon-Taylor equation for a molecular distribution [20]. When the concentration of diazepam in PVP K30 was increased, multiple $T_g s$ were observed at 51.2°C and 150.3°C for a drug load of 30% w/w, and at 45.2°C, 120.4°C and 166.7°C for a drug load of 40% w/w. These results indicate that in these solid dispersions diazepam was partially molecularly mixed with PVP K30 and partially distributed as amorphous clusters. Most likely, the size of the amorphous clusters was in the nano-meter scale [20].

Furthermore, all inulin-based solid dispersions showed one single T_g implying that diazepam was molecularly dispersed in these solid dispersions (data not shown). The

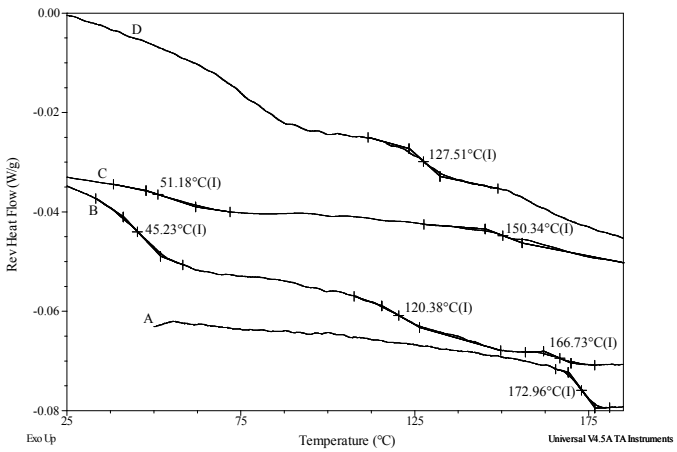

Figure 2 Reversible heat flow thermograms of (A) PVP K30, and diazepam in PVP K30-based solid dispersions at drug loads of (B) 40% w/w, (C) 30% w/w and (D) 20% w/w.

$T_g s$ were very close to those of the pure inulins and not in between the T_g of pure diazepam and pure inulin as predicted by the Gordon-Taylor equation for molecular distribution. This has been found before for inulin-based solid dispersions and was attributed to absence of interaction between the drug and the inulin [20].

3.5.4 Dissolution studies

3.5.4.1 Dissolution behavior of tablets prepared from solid dispersions and physical mixtures containing 20% w/w diazepam in PVPs

The dissolution behavior of tablets prepared from PVP-based solid dispersions and physical mixtures at a drug load of 20% w/w were evaluated. In these experiments, both the concentrations of diazepam and PVP released from these tablets were determined.

The dissolution profiles of PVP K12-based tablets are shown in Fig. 3a. For physical mixture tablet, diazepam was dissolved, as expected, slowly and after 2 h, only about 60% of the drug was dissolved. On the other hand, PVP K12 was completely dissolved within 5 min. Diazepam incorporated in solid dispersion tablets also dissolved slowly and after 2 h, only about 45% of the drug was dissolved. In contrast, dissolution of PVP K12 from solid dispersion tablets was in particular initially much faster than that of the drug and was completed after 90 min. It was unexpected that the dissolution of both diazepam and PVP K12 from physical mixture tablets was faster than that from solid dispersion tablets. However, these results can be ascribed to the fact that during dissolution, the physical mixture tablets disintegrated while the solid dispersion tablets gradually eroded which was visually observed.

The dissolution profiles of PVP K30-based tablets are presented in Fig. 3b. Diazepam from the physical mixture tablets released slowly and after 2 h, the amount of dissolved drug was only about 65%. In contrast, PVP K30 from the physical mixture tablets was completely dissolved in about 15 min. However, diazepam from the solid dispersion tablets dissolved extremely fast and was completely dissolved within 15 min. In addition, PVP K30 from solid dispersion tablets was dissolved very fast and its profile coincided with the dissolution profile of diazepam over the complete dissolution time. The dissolution profiles of PVP K60-based tablets are shown in Fig. 3c. Both diazepam and PVP K60 from the physical mixture tablets dissolved slowly. However, the dissolution rate of PVP K60 from the physical mixture tablets was higher than that of diazepam. After 2 h, about 35% of the drug was dissolved while PVP K60 was completely dissolved. In contrast, for the solid dispersion tablets showed that both dissolutions of diazepam and PVP K60 were slow and coincided.

3.5.4.2 Effect of drug load diazepam on dissolution of PVP- or inulin-based solid dispersion tablets

The dissolution profiles of the PVP K12- or K30-based solid dispersion tablets containing diazepam at different drug loads are presented in Fig. 4. As mentioned above, diazepam incorporated in PVP K12-based solid dispersion tablets at a drug

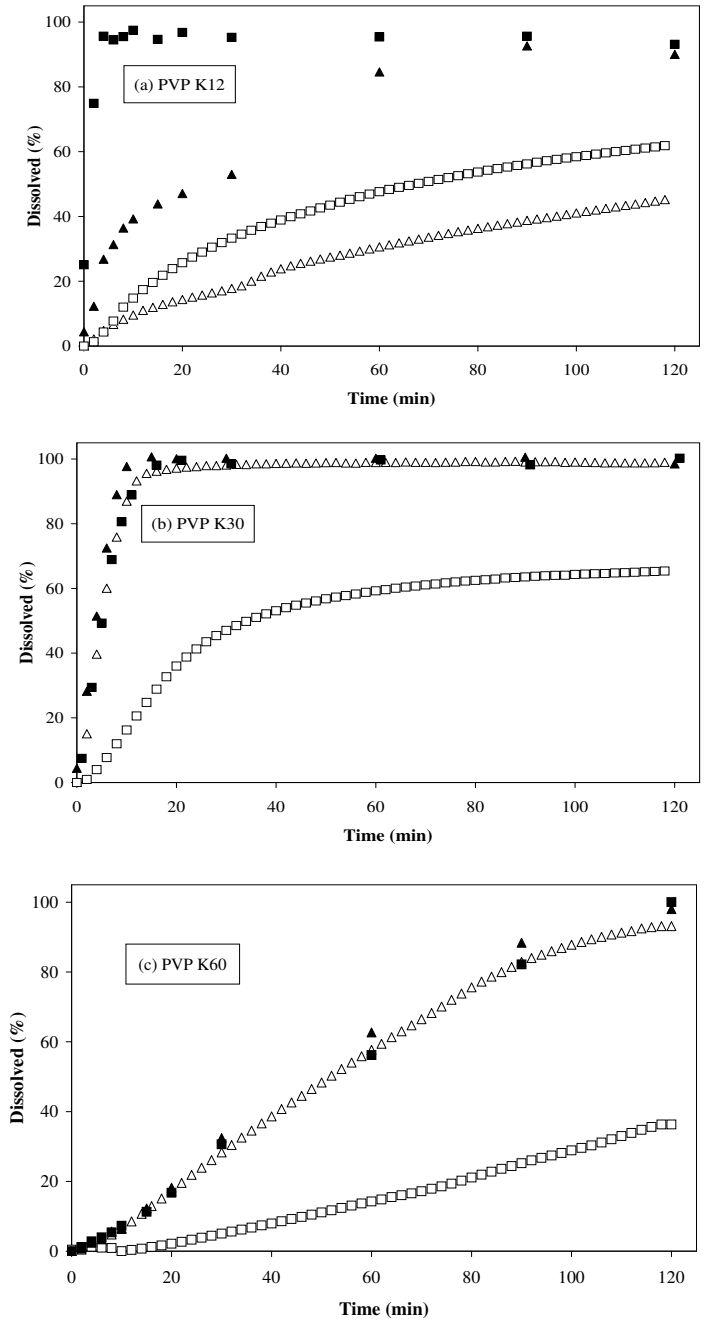

Figure 3 Dissolution of tablets prepared from solid dispersions (SD) and physical mixtures (PM) of 20% w/w diazepam in (**a**): PVP K12, (**b**): PVP K30, and (**c**): PVP K60 (Δ: diazepam from SD, ▲: PVP from SD, □: diazepam from PM and ▪: PVP from PM).

load of 20% w/w dissolved slowly. In contrast, when the drug load was reduced to 5% or 10% w/w, the dissolution was fast. Within 10 min, diazepam at a drug load of 5% w/w was completely dissolved while diazepam at a drug load of 10% w/w was dissolved for about 90%. For PVP K30-based solid dispersion tablets, again, diazepam at a drug load of 20% w/w showed extremely fast dissolution. Interestingly, when the drug load was increased to 30% w/w, the dissolution of diazepam remained very fast. About 90% of the drug was dissolved within 14 min.

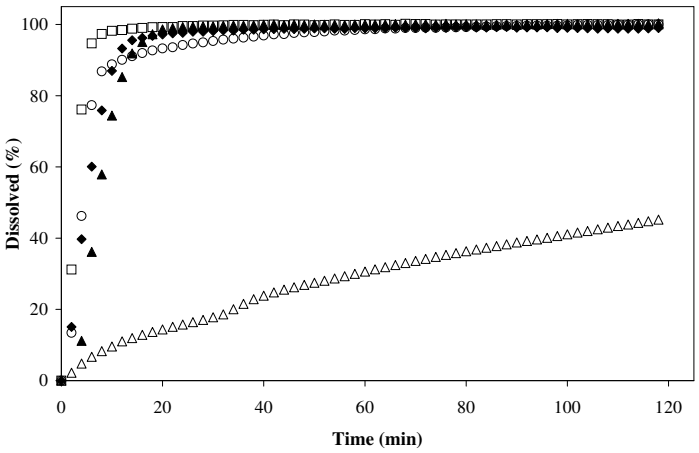

Figure 4 Dissolution of tablets prepared from PVP-based solid dispersions containing diazepam with various drug loads. (□: 5% drug load in PVP K12, ○: 10% drug load in PVP K12, Δ: 20% drug load in PVP K12, ♦: 20% drug load in PVP K30 and ▲: 30% drug load in PVP K30).

The dissolution profiles of diazepam at different drug loads in inulin 1.8 kDa-, 4 kDa- or 6.5 kDa-based solid dispersion tablets are shown in Fig. 5. At a drug load of 10% w/w in inulin 1.8 kDa-based solid dispersion tablets, diazepam initially dissolved fast as about 70% within 16 min but then slowed down and until 2 h, diazepam was completely dissolved. However, when the drug load was increased to 20% w/w, diazepam dissolved slowly. About 10% of the drug was dissolved after 25 min and it took 2 h to dissolve 90% of the drug. In addition, with inulin 4 kDa-based solid dispersion tablets containing 10% w/w diazepam, the drug was dissolved completely within 25 min. When the drug load was increased to 20% w/w, the dissolution was slower as after 25 min about 55 % of the drug was dissolved and after 1 h the drug was dissolved completely. When the drug load was further increased to 30% w/w, about 10% and 80% of the drug were dissolved within 25 min and 2 h, respectively. For inulin 6.5 kDa- based solid dispersion tablets containing 10% w/w diazepam, the drug dissolved slowly and after 2 h about 70% of the drug was dissolved. Moreover, it was found that inulin 6.5 kDa also dissolved slow (data not shown).

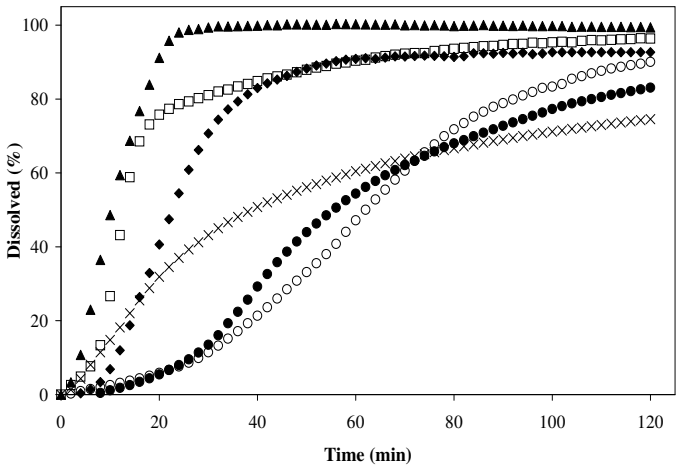

Figure 5 Dissolution of tablets prepared from inulin-based solid dispersions containing diazepam with various drug loads. (□: 10% drug load in inulin 1.8 kDa, ○: 20% drug load in inulin 1.8 kDa, ▲: 10% drug load in inulin 4 kDa, ♦: 20% drug load in inulin 4 kDa, ●: 30% drug load in inulin 4 kDa and ×: 10% drug load in inulin 6.5 kDa).

3.5.4.3 Effect of drug load nifedipine on dissolution of PVP- or inulin-based solid dispersion tablets

In this study, not only diazepam was used as a model drug but also nifedipine to check whether the trend in the dissolution behavior as described above is not specific for diazepam but also applicable to other lipophilic drug substances. Table 4 presents the time at which 80% of nifedipine was dissolved from PVP- or inulin-based solid dispersion tablets ($t_{80\%}$). At drug loads of 5% and 10% w/w nifedipine in PVP K12, the $t_{80\%}$ values were 3.4 min and 3.9 min, respectively. However, when increasing the drug load to 20% w/w nifedipine, the dissolution of the drug was very slowly with a $t_{80\%}$ value more than 2 h. After 2 h, the remaining tablet was analyzed by DSC. It appeared that the remaining tablet consisted of fully crystalline nifedipine. When using PVP K30 as carrier, even at a high drug load of 20% w/w nifedipine, the dissolution of the drug was extremely fast as the $t_{80\%}$ value was about 7 min. The percentage of dissolved nifedipine reached 100% after 16 min which remained the same until 2 h. This is quite surprising because it means that the nifedipine concentration in the dissolution medium was 20 mg/L while the saturation concentration of nifedipine is only 9 mg/L (Table 3). Therefore, it was decided to extend the dissolution experiment. It was found that after 24 h, the nifedipine concentration was decreased to about 10 mg/L. Apparently, during dissolution the dissolution medium became highly supersaturated and remained as such for at least 2 h. Thereafter, the nifedipine concentration decreased due to crystallization until the saturation concentration was reached. In the case of nifedipine in inulin-based solid dispersion tablets, only a low drug load of 5% w/w nifedipine in

Table 4 Time at which 80% of nifedipine was ($t_{80\%}$) dissolved from PVP- or inulin-based solid dispersion tablets with various drug loads.

Drug load (% w/w)	$t_{80\%}$ (min)			
	PVP K12	PVP K30	Inulin 1.8 kDa	Inulin 4 kDa
5	3.38	-	3.59	8.48
10	3.85	-	>120	>120
20	>120	7.03 [a]	-	-

[a] After 24 h of dissolution , about 50% of drug was dissolved.

inulin 1.8 kDa- or 4 kDa-based solid dispersion tablets showed fast dissolution as the $t_{80\%}$ values were about 4 min and 8.5 min, respectively. As increased drug load to 10% w/w nifedipine in these inulin carriers, the $t_{80\%}$ values were more than 2 h.

3.6 DISCUSSION

In the present study, the dissolution behavior of tablets prepared from solid dispersions with drug-carrier interaction is compared to that without such an interaction. As a model for a carrier interacting with lipophilic drugs, PVP (K12, K30 and K60) was used. While as a model for carriers that do not interact with lipophilic drugs, inulin (1.8 kDa, 4 kDa and 6.5 kDa) were used. Diazepam and nifedipine were used as a model for lipophilic drugs. The existence of interactions between the model drugs and PVP was confirmed by a substantial increase in aqueous solubility of the drugs in the presence of PVP. In contrast, lack of an effect on aqueous solubility of the drugs in the inulin solutions indicates that there is no significant interaction between the drugs and these inulins (Table 3). XRPD and (M)DSC measurements revealed that all solid dispersions evaluated in this study were fully amorphous. Therefore, a proper comparison can be made between the dissolution behavior of the tablets prepared from these solid dispersions.

Dissolution profiles of solid dispersion tablets from both types of carriers, PVP and inulin, showed similar trends. When using low molecular weight carriers, i.e. PVP K12 and inulin 1.8 kDa, diazepam or nifedipine only dissolved fast at low drug loads. Upon increasing the drug load in these carriers, dissolution of the drugs markedly slowed down. This phenomenon can be ascribed to the extremely fast dissolution of the carrier as can be seen in the case of 20% w/w diazepam incorporated in PVP K12-based solid dispersion tablets (Fig. 3a). Consequently, the concentration of the drug in the near vicinity of the dissolving tablet will be high resulting in the formation of large drug crystals which subsequently dissolve slowly. When using carriers of higher molecular weight, i.e. PVP K30, and inulin 4 kDa, fast dissolution of drug can be achieved at higher drug loads. Apparently, with higher molecular weight carriers the drug will

crystallize less easily in the near vicinity of the dissolving tablet. We propose that this phenomenon is due to the fact that with increasing molecular weight of carrier, the dissolution rate of the carrier decreases. Consequently, the concentration of the drug in the near vicinity of the dissolving tablet will be lower. Thus, higher drug loads can be applied without uncontrolled crystallization. However, there is a limitation to the increase in carrier molecular weight. When using high molecular weight carriers, i.e. PVP K60 and inulin 6.5 kDa, the drug dissolution was very slow. In this case, the slow dissolution rate was not due to uncontrolled crystallization of the drug but because of the very slow dissolution rate of the carrier. From the results above, it can be concluded that fast dissolution of drug in PVP- or inulin-based solid dispersion tablets is possible by optimizing the molecular weight of the carrier and the drug load.

Dissolution of solid dispersion tablets is considered fast when the $t_{80\%}$ value is less than 20 min. When comparing PVP K30-, and inulin 1.8 kDa- or 4 kDa-based solid dispersion tablets, fast dissolution of diazepam and nifedipine with higher drug load can be obtained from the PVP K30 carrier. Diazepam at a drug load of 30% w/w and nifedipine at a drug load of 20% w/w in PVP K30-based solid dispersion tablets meet the requirement for the fast dissolution (Fig. 4 and Table 4, respectively). In contrast, diazepam at only a drug load of 10% w/w in inulin 4 kDa carrier, and nifedipine at a drug load of 5% w/w in inulin 1.8 kDa or 4 kDa carriers meet this requirement (Fig. 5 and Table 4, respectively). Moreover, we showed that the solubilities of both diazepam and nifedipine in 10% w/v PVP solution were strongly increased. This implies that in the boundary layer of the dissolving tablet, where the concentration of PVP will be high, the saturation concentration of the drug will be much higher than in the bulk of the dissolution medium. Consequently, the drug concentration in these boundary layers can be high without recrystallization to occur. PVP dissolved from these solid dispersion tablets will not significantly increase the saturation concentration of drug in the bulk of dissolution medium because the concentration of PVP in the dissolution medium is less than 0.1% w/v. In contrast, in the 5% w/v inulin solutions, the solubility of diazepam or nifedipine was not increased implying that the saturation concentration of the drug in the boundary layer of dissolving tablet is the same as in the bulk of the dissolution medium. Therefore, when increasing the drug load, the tendency to recrystallization of the drug in the near vicinity of dissolving tablets is higher in the case of inulin-based solid dispersion tablets than in the case of PVP-based solid dispersion tablets. In conclusion, when high drug loads have to be applied, solid dispersions in which drug and carrier do interact are preferred over those in which drug and carrier do not interact.

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CHAPTER 4

STRONGLY ENHANCED DISSOLUTION RATE OF FENOFIBRATE SOLID DISPERSION TABLETS BY INCORPORATION OF SUPERDISINTEGRANTS

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4.1 ABSTRACT

In this study, it was shown that the incorporation of superdisintegrants in solid dispersion tablets containing a high drug load can strongly enhance the dissolution rate of the highly lipophilic drug fenofibrate. In addition, the dissolution rate was more increased when the superdisintegrant was incorporated in the drug containing solid dispersions than when it was physically mixed with the solid dispersions. The dissolution rate enhancement strongly depended on the type of superdisintegrant and increased in the order: Polyplasdone® XL-10 < Polyplasdone® XL << Ac-Di-Sol® ≈ Primojel®. The dissolution behavior also depended on the type of hydrophilic carrier. Solid dispersion tablets based on inulin 4 kDa, polyethylene glycol 20K and polyvinylpyrrolidone K30 showed a much faster dissolution than those based on mannitol and hydroxypropyl-β-cyclodextrin. Finally, inulin 4 kDa-based solid dispersion tablets showed an excellent storage stability while polyethylene glycol 20K- and polyvinylpyrrolidone K30-based solid dispersion tablets did not.

4.2 INTRODUCTION

Solid dispersion technology can be applied to increase the dissolution rate of highly lipophilic drugs thereby improving their bioavailability [1-4]. Usually, solid dispersions are two component systems consisting of a hydrophilic carrier in which the drug is incorporated. The drug incorporated in the hydrophilic carrier may be molecularly dispersed or may occur as nanocrystals or amorphous nano-particles. The improved dissolution rate of the drug can be ascribed to i) an increased solubility of the drug because of its amorphous state or small particle size (Kelvin's law) [5-8] ii) an increasing surface area available for drug dissolution because of the small size of the drug particles [9,10] and iii) an improved wetting of the drug caused by the hydrophilic carrier [11,12].

In a previous study, we investigated the dissolution behavior of solid dispersion tablets in which lipophilic drugs were incorporated in saccharide carriers. The dissolution of solid dispersion tablets was rapid when the carrier did not dissolve very slow or very fast and when a drug was incorporated in the carrier at a relatively low drug load. Obviously, when the carrier dissolves slowly, the drug will also dissolve slowly. However, the slow dissolution rate of the drug when using fast dissolving carriers and/or formulations with high drug loads was considered less obvious. We hypothesized that during dissolution of these tablets the concentration of the drug in the near vicinity of the tablets became so high that uncontrolled crystallization of the drug occurred. Consequently, large drug crystals are formed which will dissolve slowly. This hypothesis was tested by analysis of remnants of the tablets which were taken out of the dissolution vessel after two hours of dissolution. Indeed, these remnants consisted of pure drug which was fully crystalline [13]. Therefore, we investigated the effect of incorporating a surfactant, sodium lauryl sulfate (SLS), in solid dispersions on the dissolution behavior. It was expected that during dissolution the high surfactant concentration in the near vicinity of the dissolving tablet would increase the drug solubility and thereby prevent crystallization of the drug. Indeed, it was found that the incorporation of SLS in solid dispersions strongly improved the dissolution rate of solid dispersions with a high drug load [14]. However, the amount of SLS incorporated in such solid dispersions had to be rather high which may lead to irritation of the gastro-intestinal tract.

Another interesting method to improve the dissolution of solid dispersion tablets with a high drug load might be the incorporation of superdisintegrants in the solid dispersions because superdisintegrants do not irritate the gastro-intestinal tract and can be used at low amounts in the formulations. We speculate that by the incorporation of superdisintegrants, the tablets will rapidly disintegrate which prevents crystallization of the drug. Therefore, in the present study we have investigated the effects of the following variables on dissolution behavior of solid dispersion tablets containing superdisintegrants: i) the way to incorporate superdisintegrants in solid dispersion

tablets, ii) the type of superdisintegrant incorporated in solid dispersion tablets, and iii) the type of hydrophilic carrier. In addition, the storage stability of some selected solid dispersion tablets was investigated. Fenofibrate was used a model drug. Sodium starch glycolate (Primojel®), croscarmellose sodium (Ac-Di-Sol®) and two types of crosslinked PVP (Polyplasdone® XL and XL-10) were used as superdisintegrants. Inulin 4 kDa, polyvinylpyrrolidone (PVP) K30, polyethylene glycol 20 kDa (PEG 20K), mannitol and hydroxypropyl-beta-cyclodextrin (HP-β-CD) were used as hydrophilic carriers.

4.3 MATERIALS

The following materials were used as supplied: fenofibrate and HP-β-CD from Sigma-Aldrich Chemie GmbH, Steinheim, Germany; inulin 4 kDa from Sensus, Roosendaal, The Netherlands; crosslinked PVP (Polyplasdone® XL and XL-10) from ISP, Wayne, USA: PVP K30 and SLS from BUFA B.V. Uitgeest, The Netherlands; PEG 20K and tertiary butyl alcohol (TBA) from Fluka Chemie GmbH, Steinheim, Germany; mannitol (Pearlitol® SD) from Roquette, Lestrem, France; sodium starch glycolate (Primojel®) from DMV International, Veghel, The Netherlands; croscarmellose sodium (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH-102) from FMC Biopolymer, Philadelphia, USA. Lipanthyl® tablets (145 mg fenofibrate tablets, Lot no. 12178, Expiry 12/2011) were purchased from Laboratoires Fournier S.A., Dijon Cedex, France. Demineralized water was used in all experiments.

4.4 METHODS

Three different types of formulations were prepared: 1) solid dispersions composed of drug and carrier in which superdisintegrants were incorporated; 2) solid dispersions composed of drug and carrier physically mixed with superdisintegrants; 3) physical mixtures of drug, carrier and superdisintegrant.

4.4.1 Superdisintegrants incorporated in solid dispersions

Solid dispersions were prepared by lyophilization as described before [15]. Briefly, fenofibrate was dissolved in pure TBA at a concentration of 12.5 mg/mL. Inulin 4 kDa, PVP K30, PEG 20K, HP-β-CD or mannitol were dissolved in demineralized water at a concentration of 8.33 mg/mL. The superdisintegrants were dispersed in the aqueous solutions at a concentration of 0.696 mg/mL. Subsequently, these two solutions were mixed at a TBA/water ratio of 4/6 (v/v). The final concentrations of drug, carrier and superdisintegrant in the water/TBA mixture were 5, 5 and 0.42 mg/mL, respectively. Immediately after mixing, the solution was frozen in liquid nitrogen and then lyophilized. The formed solid dispersions all consisted of 48% w/w fenofibrate, 48% w/w carrier and 4% w/w superdisintegrant.

In a typical lyophilization cycle, the frozen solution was placed on the shelf of a Christ model Alpha 2-4 lyophilizer (Salm and Kipp, Breukelen, The Netherlands) with

a condenser temperature of -85°C. Lyophilization was performed according to a two-step procedure. Firstly, the pressure was set at 0.220 mbar and the shelf temperature at -35°C for one day. Subsequently, the pressure was decreased to 0.05 mbar, while the shelf temperature was gradually increased to 20°C. This condition was maintained for another day. After removing the samples from lyophilizer, they were placed in a desiccator over silica gel for at least one day before performing further experiments.

4.4.2 Superdisintegrants physically mixed with solid dispersions

For solid dispersions composed of drug and carrier physically mixed with superdisintegrants only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. Firstly, solid dispersions consisted of 50% w/w fenofibrate and 50% w/w inulin 4 kDa were prepared by lyophilization as described above. Thereafter, Primojel® and solid dispersions were gently mixed by using a spatula and mortar. The final powder mixture was composed of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. A solid dispersion without superdisintegrant at a drug load of 50% w/w was used as a control. The samples were stored at the same conditions as described in Section 4.4.1.

4.4.3 Preparation of fully physical mixture

For fully physical mixtures only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. Fenofibrate, inulin 4 kDa and Primojel® were gently mixed by using a spatula and mortar. The powder mixture consisted of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. The samples were stored at the same conditions as described in Section 4.4.1.

4.4.4 Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC Q2000, TA Instruments, Ghent, Belgium) was used to determine the degree of drug crystallinity in solid dispersions. About 2-4 mg of sample in an open aluminium standard pan was heated at a scanning rate of 20°C/min from a temperature -50 to 220°C under a nitrogen gas flow. The heat of fusion of crystallized drug in solid dispersions was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was measured in a separate experiment. The ratio of the two fusion enthalpies was used to calculate the extent of relative drug crystallinity in solid dispersions. All experiments were conducted at least in duplicate. Calibrations of temperature and heat flow were carried out with indium.

4.4.5 X-ray powder diffraction (XRPD)

Samples were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, The Netherlands) with a copper anode (Cu Kα radiation, λ= 0.15405 nm, 40 kV, 40 mA). The diffraction pattern was measured with a step size of 0.008° and a dwell time of 45 s at each step between 4-50 2θ at ambient temperature.

4.4.6 Tableting

All powder combinations were compressed to flat and round tablets using an ESH compaction apparatus (Hydro Mooi, Appingedam, The Netherlands). Tablets containing 48 mg fenofibrate were prepared at a maximum force of 5 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 100 mg and 9 mm, respectively. Tablets containing the 145 mg drug were prepared at a maximum force of 10 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 302 mg or 640 mg and 13 mm, respectively. The 302 mg tablets were prepared from an inulin 4 kDa based solid dispersion with Primojel® incorporated (145 mg fenofibrate, 145 mg inulin 4 kDa and 12 mg Primojel®). The 640 mg tablets were prepared from the same both amount and type of solid dispersion which was physically mixed with 338 mg Avicel® PH-102.

4.4.7 Disintegration test

The disintegration time of the tablets was determined in 900 mL of 0.5% w/v SLS at 37°C using a USP disintegration test apparatus without disc (Erweka Apparatebau-GmbH, Heusenstamn Kr. Offenbach/Main, Germany). The samples were tested in triplicate.

4.4.8 Dissolution experiments

Dissolution of samples was carried out by using a USP dissolution apparatus II (Rowa Techniek, Leiderdorp, The Netherlands) with a paddle at 100 rpm and 37°C. The dissolution medium was continuously circulated through UV-spectrophotometer flow cells (Model Ultraspec III; Pharmacia LKB, Uppsala, Sweden) at 20 mL/min using a peristaltic pump (Ismatec, Zurich, Switzerland). The samples were filtered through 0.35 μm filter prior to analysis. Concentration of fenofibrate in dissolution medium was measured every 2 min for 2 h at a wavelength of 290 nm. Measurements were conducted in triplicate. To maintain sink condition during dissolution test, one liter of demineralized water containing 0.5% w/v SLS and 1.5% w/v SLS was used as dissolution mediums for the tablets containing 48 mg and 145 mg fenofibrate, respectively.

4.4.9 Stability study

Solid dispersion tablets were stored under closed vial conditions in climate chambers at 40°C/75% relative humidity (RH) and 20°C/45%RH for 3 months. The dissolution behavior of these tablets was evaluated in triplicate.

4.4.10 Comparison of dissolution profiles

Dissolution profiles were compared by using similarity factor (f_2). The f_2 is defined by the following equation [16]:

$$f_2 = 50 \log\{[1+1/n \sum n_{t=1}(R_t-T_t)^2]^{-0.5} \times 100\}$$

where n is the number of dissolution sampling times, and R_t and T_t are the percent dissolved at each time point for the reference and test products, respectively. An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

4.5 RESULTS

4.5.1 DSC studies

The melting point and the melting enthalpy of crystalline fenofibrate were 81.0°C and 91.0 J/g, respectively. The glass transition temperature (T_g) of amorphous fenofibrate was -19.6°C. The degree of relative crystallinity of fenofibrate in all formulations except for the PEG 20K-based solid dispersion is presented in Table 1. The relative degree of crystallinity of the drug in the PEG 20K-based solid dispersion could not be determined because its corresponding physical mixture did not give an appropriate thermogram. The thermogram lacked the melting peak of fenofibrate most likely

Table 1 Degree of relative fenofibrate crystallinity in various formulations (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulations	**Relative crystallinity of fenofibrate (%) mean ± s.d.**
Way in which Primojel® was incorporated in inulin 4 kDa- based formulations	
Primojel® incorporated in SD	70.83 ± 3.01
Primojel® physically mixed with SD	73.24 ± 0.91
Fully PM	99.91 ± 2.28
No Primojel® incorporated in SD	72.90 ± 3.36
Type of superdisintegrant incorporated in inulin-based SDs	
Primojel®	70.83 ± 3.01
Ac-Di-Sol®	70.34 ± 0.70
Polyplasdone® XL	70.50 ± 0.89
Polyplasdone® XL-10	73.32 ± 4.13
Type of carrier incorporated in the solid dispersion. Primojel® was incorporated in all solid dispersions.	
Inulin 4 kDa	70.83 ± 3.01
PEG 20K	N/A[a]
PVP K30	73.28 ± 0.26
HP-β-CD	66.56 ± 1.31
Mannitol	83.48 ± 0.79

[a] Could not be determined by differential scanning calorimetry.

because the drug dissolved in PEG K20 after the carrier was molten (at 60°C). In all other solid dispersions, except for the mannitol-based solid dispersion, about 66%-73% of fenofibrate was crystalline. The extent of relative drug crystallinity in the mannitol carrier was approximately 83%. Moreover, besides the endothermic peak of fenofibrate the thermogram of the mannitol-based solid dispersion showed an endothermic peak at 164.8°C which can be ascribed to the melting of crystalline mannitol. In none of the thermograms of the solid dispersions the T_g of fenofibrate was found. These results indicate that fenofibrate in these solid dispersions was partially present as crystals and partially molecularly distributed.

4.5.2 XRPD studies

Fig. 1 shows the X-ray powder diffraction patterns of pure fenofibrate, inulin 4 kDa-based solid dispersion in which Primojel® was incorporated, inulin 4 kDa-based solid dispersion which was physically mixed with Primojel®, its corresponding fully physical mixture and inulin 4 kDa-based solid dispersion without Primojel®. The X-ray powder diffraction pattern of pure fenofibrate showed peaks which are consistent to the results by Heinz et al. [17]. The typical peak intensities of fenofibrate in the fully physical mixture were higher than those of the inulin 4 kDa-based solid dispersions with Primojel® incorporated or physically mixed and the inulin 4 kDa-based solid dispersion without Primojel®. In addition, the X-ray powder diffraction pattern of all solid dispersions in which different superdisintegrants were incorporated showed the typical diffraction pattern of crystalline fenofibrate (Fig. 2). X-ray diffraction patterns of Primojel®, Ac-Di-Sol®, Polyplasdone® XL and XL-10 indicate that these superdisintegrants were amorphous. Finally, X-ray powder diffraction patterns of solid dispersions composed of fenofibrate, Primojel® and different carriers, pure carrriers and pure fenofibrate are presented in Fig. 3. The pure carriers HP-β-CD, PVP K30 and inulin 4 kDa showed no diffraction peaks, indicating that they were amorphous, while PEG 20K and mannitol did show diffraction peaks indicating these carriers were (partially) crystalline. HP-β-CD-, PVP K30- and inulin 4 kDa-based solid dispersions only showed the typical peaks of crystalline fenofibrate. X-ray powder diffraction patterns of PEG 20K- and mannitol-based solid dispersions, however, showed diffraction peaks which were the same as those of the pure carriers and fenofibrate. In conclusion, during manufacturing of all solid dispersions, fenofibrate at least partially crystallized. In addition, the carriers PEG 20K and mannitol also crystallized while the other carriers were amorphous. These findings are consistent with the DSC results.

4.5.3 Disintegration studies

The disintegration time of the various tablet formulations in 0.5% w/v SLS is shown in Table 2. The inulin 4 kDa-based solid dispersion tablets without Primojel® incorporated showed an extremely slow disintegration of about 100 min. When Primojel® was incorporated either in the inulin 4 kDa-based solid dispersions or physically mixed with

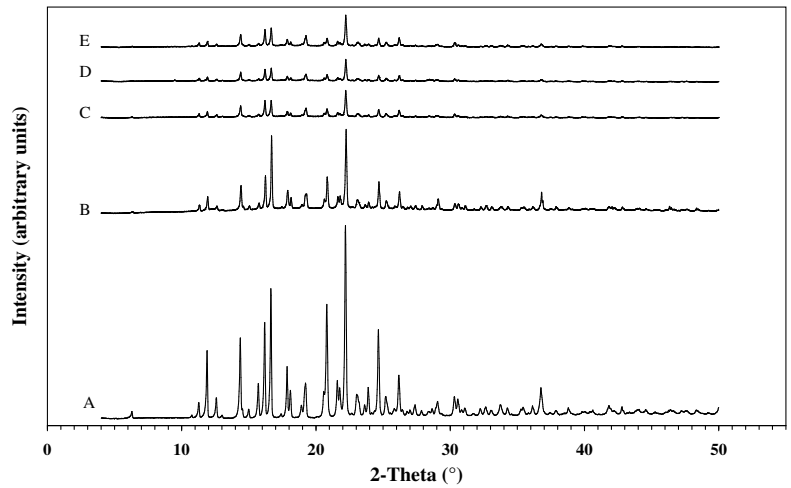

Figure 1 X-ray powder diffraction patterns of (A) fenofibrate, (B) fully physical mixture of fenofibrate, inulin 4 kDa and Primojel®, (C) solid dispersion (SD) of fenofibrate and inulin 4 kDa physically mixed with Primojel®, (D) SD of fenofibrate, inulin 4 kDa and Primojel® and (E) SD of fenofibrate and inulin 4 kDa without Primojel®.

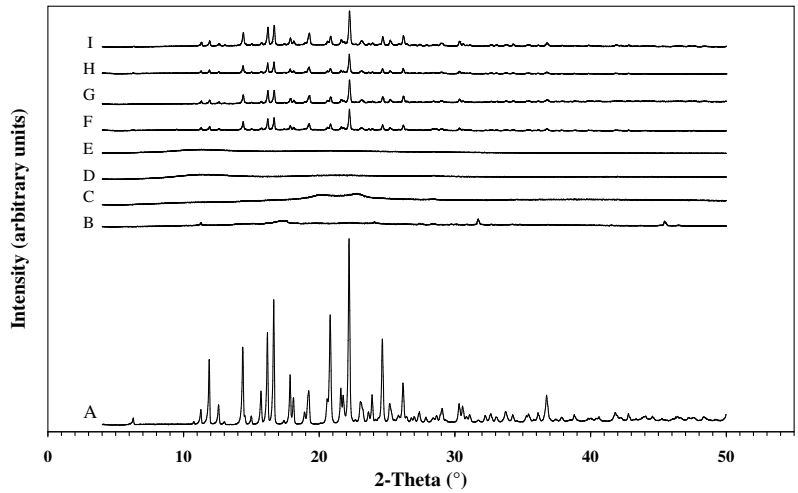

Figure 2 X-ray powder diffraction patterns of (A) fenofibrate, (B) Primojel®, (C) Ac-Di-Sol®, (D) Polyplasdone® XL, (E) Polyplasdone® XL-10, (F) solid dispersion (SD) of fenofibrate, inulin 4 kDa and Primojel®, (G) SD of fenofibrate, inulin 4 kDa and Ac-Di-Sol®, (H) SD of fenofibrate, inulin 4 kDa and Polyplasdone® XL and (I) SD of fenofibrate, inulin 4 kDa and Polyplasdone® XL-10.

the inulin 4 kDa-based solid dispersion, the disintegration time was strongly reduced to 10-11 min. Remarkably, the fully physical mixture tablets composed of inulin 4 kDa, Primojel® and fenofibrate disintegrated even faster, with disintegration time of

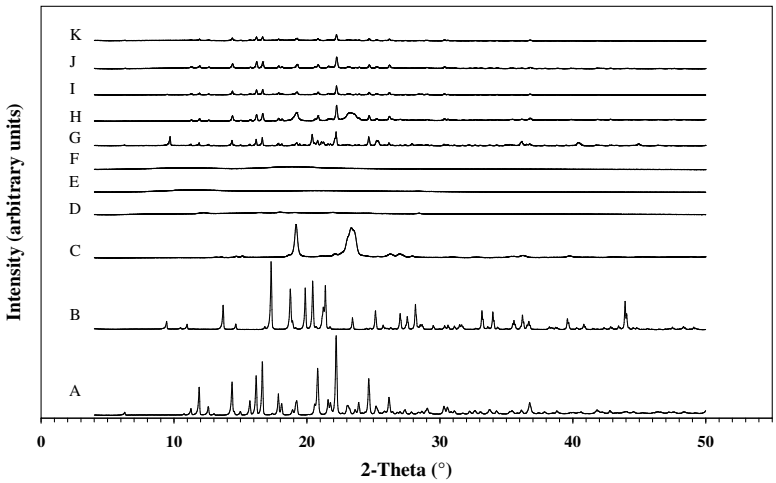

Figure 3 X-ray powder diffraction patterns of (A) fenofibrate, (B) mannitol, (C) PEG 20K, (D) inulin 4 kDa, (E) PVP K30, (F) HP-β-CD, (G) solid dispersion (SD) of fenofibrate, Primojel® and mannitol, (H) SD of fenofibrate, Primojel® and PEG 20K, (I) SD of fenofibrate, Primojel® and inulin 4 kDa, (J) SD of fenofibrate, Primojel® and PVP K30 and (K) SD of fenofibrate, Primojel® and HP-β-CD.

8 min. When different superdisintegrants were incorporated in inulin 4 kDa, tablets containing Primojel® and Ac-Di-Sol® gave more or less the same disintegration times. In contrast, tablets with Polyplasdone® XL and XL-10 incorporated gave disintegration times of about 24 and 31 min, respectively. Furthermore, when different carriers in which Primojel® was incorporated were used, disintegration time of tablets containing the carriers inulin 4 kDa, PEG 20K and PVP K30 were about 9-11 min. Disintegration of tablets prepared from mannitol- and HP-β-CD-based solid dispersions was extremely fast with disintegration time of about 2 and 4 min, respectively.

4.5.4 Dissolution studies

First, the effect of the presence and the way of incorporation of Primojel® on the dissolution behavior of tablets containing inulin 4 kDa as carrier was investigated (Fig. 4). As expected, dissolution of solid dispersion tablets without Primojel® was extremely slow. Only about 7% of the drug was dissolved within 20 min and about 55% after 2 h. After this dissolution test, the remnants of the tablets were analyzed by DSC and appeared to consist of fully crystalline fenofibrate. Dissolution of fully physical mixture tablets was faster than that of the solid dispersion tablets without Primojel®. The dissolution of drug was initially rapid but then slowed down. After 2 h only about 65% of the drug was dissolved. When Primojel® was incorporated in the solid dispersion the drug dissolved very fast and over 80% of the drug was released within 20 min. The drug was completely dissolved within 30 min. Finally, when Primojel® was physically

Table 2 Disintegration time of physical mixture tablets and various solid dispersion tablets in 0.5% w/v SLS (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulations	**Disintegration time (min) mean ± s.d.**
Way in which Primojel® was incorporated in inulin 4 kDa-based formulations	
Primojel® incorporated in SD	10.35 ± 0.25
Primojel® physically mixed with SD	11.16 ± 0.47
Fully PM	8.23 ± 0.44
No Primojel® incorporated in SD	101.55 ± 1.33
Type of superdisintegrant incorporated in inulin-based SDs	
Primojel®	10.35 ± 0.25
Ac-Di-Sol®	12.07 ± 0.57
Polyplasdone® XL	24.02 ± 0.50
Polyplasdone® XL-10	30.59 ± 0.29
Type of carrier incorporated in the solid dispersion. Primojel® was incorporated in all solid dispersions.	
Inulin 4 kDa	10.35 ± 0.25
PEG 20K	9.07 ± 0.32
PVP K30	10.41 ± 0.20
HP-β-CD	4.37 ± 0.22
Mannitol	1.41 ± 0.26

mixed with the solid dispersion, about 80% of the drug was dissolved within 36 min and the drug was completely dissolved within 1 h. When the dissolution profile of tablets composed of inulin 4 kDa-based solid dispersion with Primojel® incorporated is compared to those tablets composed of inulin 4 kDa-based solid dispersion with Primojel® physically mixed, the corresponding fully physical mixture and inulin 4 kDa-based solid dispersion without superdisintegrant, all f_2 values were less than 50, indicating the dissimilar dissolution profiles (Table 3). Because the results above indicated that solid dispersion tablets in which Primojel® was incorporated was the best formulation strategy to increase dissolution rate of fenofibrate, the dissolution behavior of solid dispersion tablets with different types of superdisintegrants incorporated in the solid dispersion were evaluated. As can be seen in Fig. 5 and Table 3, Ac-Di-Sol® had a similar effect on the dissolution behavior as Primojel® ($f_2 > 50$). In the cases of two types of Polyplasdone®, however, dissolution of fenofibrate was slow. Tablets with Polyplasdone® XL incorporated gave a slightly faster drug dissolution than tablets with Polyplasdone® XL-10 incorporated. About 80% of the drug was dissolved within 84 min and 102 min for Polyplasdone® XL and XL-10 incorporated, respectively. In both cases, at 2 h the

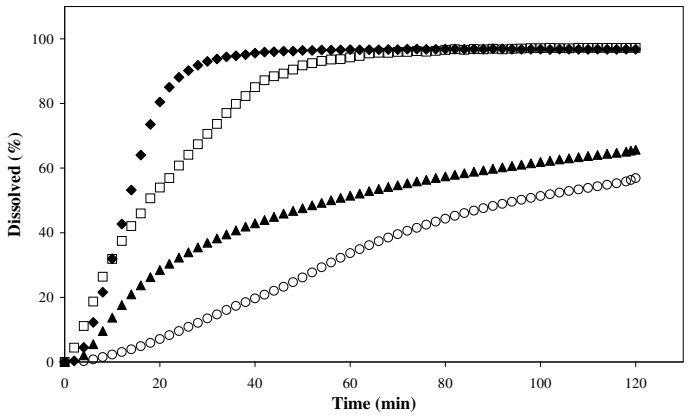

Figure 4 Dissolution of fenofibrate from inulin 4 kDa-based tablets in which Primojel® was incorporated in different ways. (♦ Primojel® incorporated in solid dispersion by freeze drying: □ Primojel® physically mixed with solid dispersion: ▲ fully physical mixture: ○ solid dispersion without Primojel®).

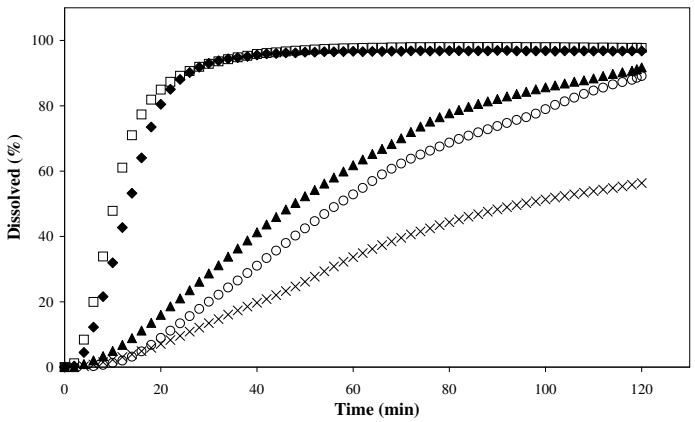

Figure 5 Dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets. Various superdisintegrants were incorporated in the solid dispersions (♦ Primojel®: □ Ac-Di-Sol®: ▲ Polyplasdone® XL: ○ Polyplasdone® XL-10: × solid dispersion tablets without superdisintegrant).

dissolution of drug was about 90%. Consequently, it can be concluded that superior dissolution behavior was achieved when Primojel® or Ac-Di-Sol® was incorporated in inulin 4 kDa-based solid dispersions instead of the two types of Polyplasdone®.

Also the effect of the types of carriers on the dissolution behavior was evaluated. As can be clearly seen in Fig. 6, inulin 4 kDa, PEG 20K and PVP K30 performed better than HP-β-CD and mannitol. About 80% of the drug was dissolved from inulin 4 kDa-,

Table 3 Similarity factor (f_2) for dissolution profiles of different formulations (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulations	Inulin 4 kDa-based SD with Primojel® incorporated (containing 48 mg fenofibrate)	Inulin 4 kDa-based SD without super-disintegrant[a]	Lipanthyl® tablet (containing 145 mg fenofibrate)
Way in which Primojel® was incorporated in inulin 4 kDa-based formulations (containing 48 mg fenofibrate)			
Primojel® incorporated in SD	—	13	—
Primojel® physically mixed with SD	43	—	—
Fully PM	21	—	—
No Primojel® incorporated in SD [a]	13	—	—
Type of superdisintegrant incorporated in inulin-based SDs (containing 48 mg fenofibrate)			
Ac-Di-Sol®	51	12	—
Polyplasdone® XL	21	32	—
Polyplasdone® XL-10	18	38	—
Type of carrier incorporated in the SD. Primojel® was incorporated in all SDs. (containing 48 mg fenofibrate)			
PEG 20K	47	—	—
PVP K30	38	—	—
HP-β-CD	23	—	—
Mannitol	19	—	—
Inulin 4 kDa-based SD with Primojel® incorporated (containing 145 mg fenofibrate)	—	—	33
PM of inulin 4 kDa-based SD with Primojel® incorporated and Avicel® PH-102 (containing 145 mg fenofibrate)	—	—	71

[a] Inulin 4 kDa-based solid dispersion without superdisintegrant containing 50 mg fenofibrate.

PEG 20K-, PVP K30-based tablets within 20, 30 and 40 min, respectively while the amount of drug released from HP-β-CD- and mannitol-based tablets was only 75% and 70% after 2 h, respectively. When the dissolution profiles of the inulin 4 kDa-base solid dispersion tablets were compared with the other carrier-based solid dispersion tablets, all f_2 values were less than 50, indicating the dissimilar dissolution profiles (Table 3). The remnants of the HP-β-CD- and mannitol-based solid dispersion tablets after 2 h dissolution were analyzed by DSC. They appeared to consist of fully crystalline of drug.

In summary, tablets prepared from inulin 4 kDa-based solid dispersions with either Primojel® or Ac-Di-Sol® incorporated showed the excellent dissolution behavior.

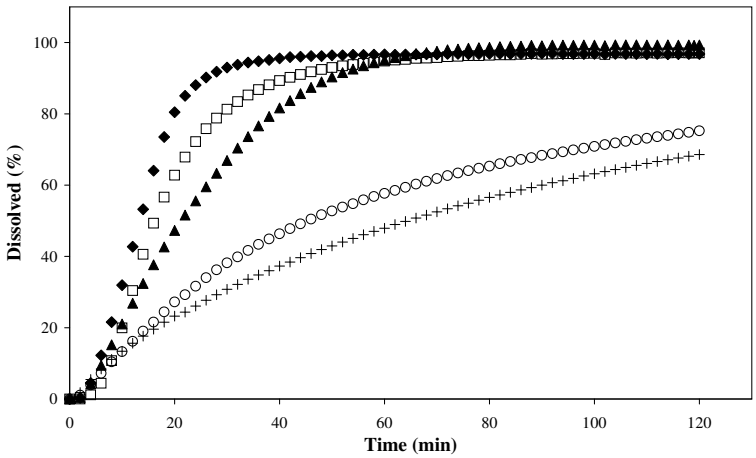

Figure 6 Dissolution of fenofibrate from solid dispersion tablets based on various carriers. In all cases Primojel® was incorporated in the solid dispersion (♦ Inulin 4 kDa: □ PEG 20K: ▲ PVP K30: ○ HP-β-CD: + mannitol).

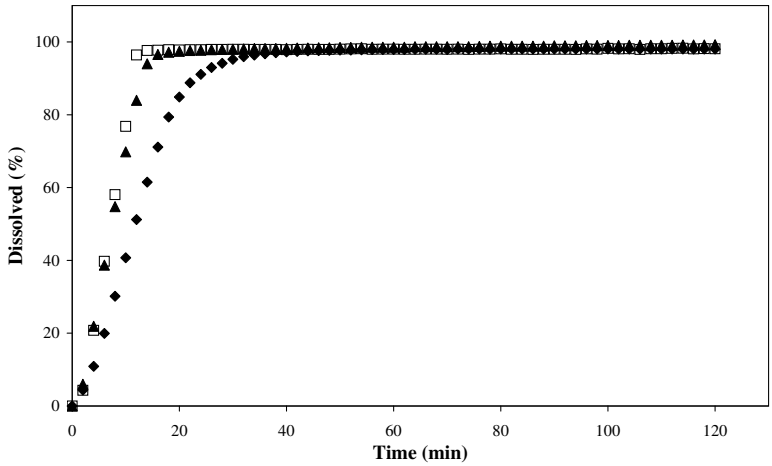

Figure 7 Dissolution of 145 mg fenofibrate tablets (♦ inulin 4 kDa-based solid dispersion (SD) with Primojel® incorporated: ▲ physical mixture of inulin 4 kDa-based SD with Primojel® incorporated and Avicel® PH-102: □ Lipanthyl®).

However, these tablets contained 48 mg fenofibrate while the marketed product, Lipanthyl® (tablets containing fenofibrate nanoparticles), contained 145 mg fenofibrate. Therefore, tablets containing 145 mg fenofibrate were prepared from inulin 4 kDa-based solid dispersions with Primojel® incorporated. In addition, tablets containing 145

mg fenofibrate were prepared from of a physical mixture of the same solid dispersion and Avicel® PH-102. As shown in Fig. 7, the dissolution of fenofibrate from the solid dispersion tablets without Avicel® PH-102 was slightly slower than from the Lipanthyl® tablets (f_2 < 50; Table 3). However, the dissolution behavior of the solid dispersion tablets with Avicel® PH-102 and that of Lipanthyl® tablets was similar (f_2 > 50; Table 3).

4.5.5 Stability studies

As described in Section 4.5.4, tablets prepared from inulin-based solid dispersion with either Primojel® or Ac-Di-Sol® incorporated and PEG K20 and PVP K30 based solid dispersions with Primojel® incorporated showed excellent dissolution behavior. Therefore, these tablet formulations were subjected to a stability study. The dissolution behavior of freshly prepared solid dispersion tablets were compared with those stored at 40ºC/75%RH or 20ºC/45%RH for 3 months.

Unexpectedly, the inulin 4 kDa-based tablets with Primojel® incorporated dissolved slightly faster after storage than when they were freshly prepared (Fig. 8a; f_2 < 50). However, the dissolution behavior of the inulin 4 kDa-based tablets with Ac-Di-Sol® incorporated was not affected by storage (Fig. 8b; f_2 > 50). Finally, the dissolution rate of the PVP K30- or PEG 20K-based tablets was significantly decreased after storage (Fig. 8c-8d; f_2 < 50). All f_2 values are shown in Table 4.

4.6 DISCUSSION

This study clearly shows that the incorporation of superdisintegrants in solid dispersion tablets can strongly increase the dissolution rate of lipophilic drugs. However, the improved dissolution behavior of the drug can only be achieved with the proper way of incorporation of the superdisintegrant in the tablets and with the proper choice of the type of superdisintegrant and carrier. As can be seen in Fig. 4, Primojel® can be used to increase dissolution rate of fenofibrate incorporated in inulin 4 kDa-based solid dispersion tablets. In addition, the dissolution rate was more increased when Primojel® was incorporated in inulin 4 kDa-based solid dispersion than when it was physically mixed with inulin 4 kDa-based solid dispersion. This might be caused by a more homogeneous distribution of Primojel® over the tablet prepared from the inulin 4 kDa solid dispersion in which Primojel® was incorporated. Furthermore, application of all four superdisintegrants evaluated in this study improved the dissolution behavior of the inulin 4 kDa based solid dispersion tablets (Fig. 5). However, the incorporation of Primojel® or Ac-Di-Sol® in the inulin 4 kDa-based solid dispersions was much more effective than the incorporation of Polyplasdone® XL or XL-10. For these inulin 4 kDa-based solid dispersion tablets, the dissolution behavior can be related to their disintegration time: a shorter disintegration time leads to a higher dissolution rate. Obviously, a rapid disintegration of inulin 4 kDa-based tablets results in an increased dissolving surface area of the drug and thereby in an increased dissolution rate. Because

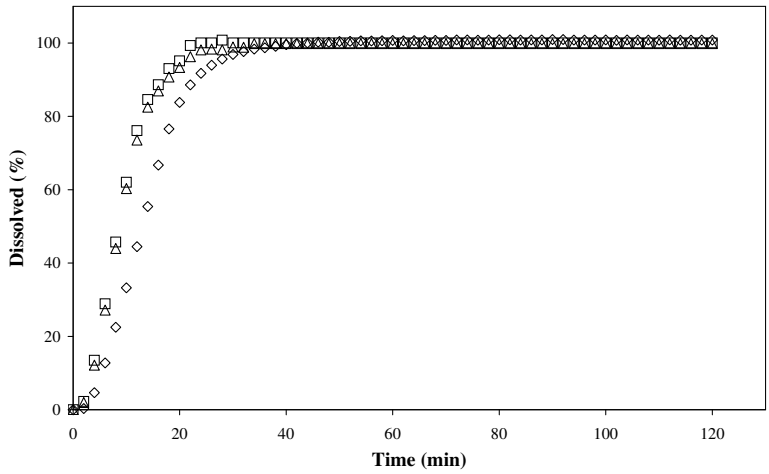

Figure 8a Effect of storage on the dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion. (◊ freshly prepared: Δ stored at 20°C/45%RH for 3 months: □ stored at 40°C/75%RH for 3 months).

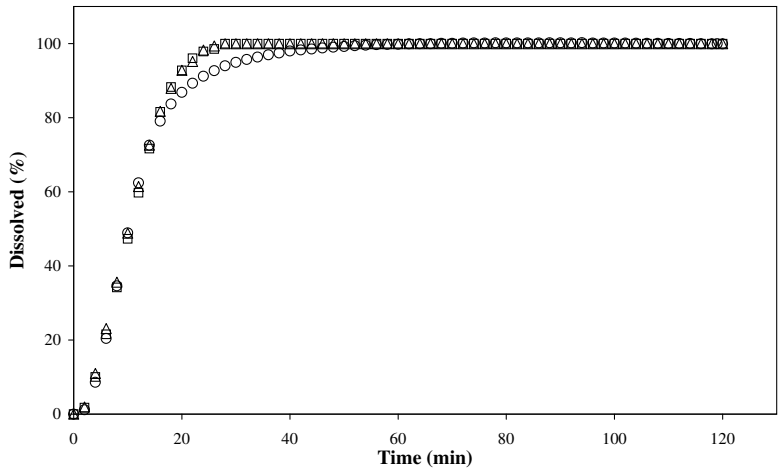

Figure 8b Effect of storage on the dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets containing Ac-Di-Sol®. Ac-Di-Sol® was incorporated in the solid dispersion. (○ freshly prepared: Δ stored at 20°C/45%RH for 3 months: □ stored at 40°C/75%RH for 3 months).

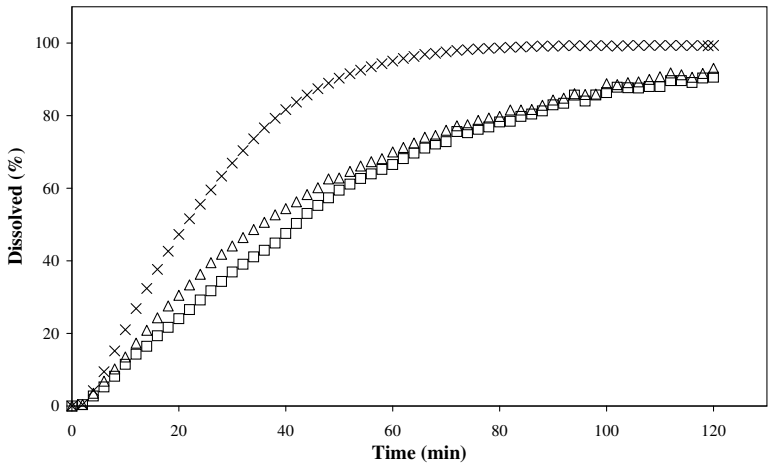

Figure 8c Effect of storage on the dissolution of fenofibrate from PVP K30-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion. (× freshly prepared: Δ stored at 20°C/45%RH for 3 months: □ stored at 40°C/75%RH for 3 months).

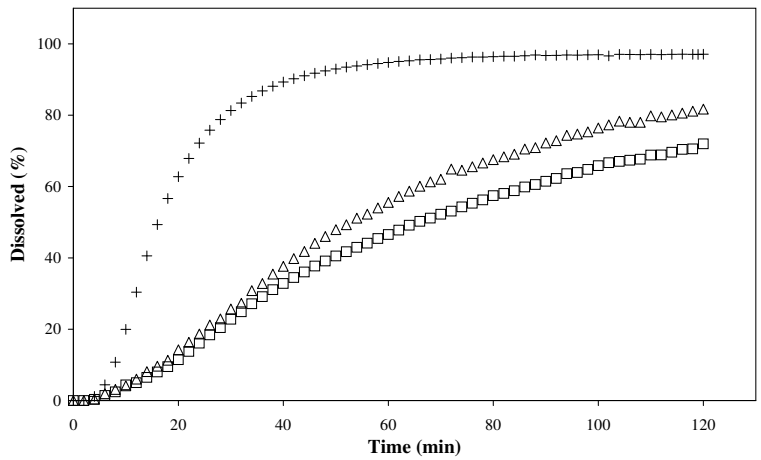

Figure 8d Effect of storage on the release of fenofibrate from PEG 20K-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion. (+ freshly prepared: Δ stored at 20°C/45%RH for 3 months: □ stored at 40°C/75%RH for 3 months).

Table 4 Similarity factor (f_2) for dissolution profiles of solid dispersion tablets freshly prepared and at storage conditions (solid dispersion is abbreviated as SD).

Formulations	Storage conditions for 3 months	
Freshly prepared	**40°C/75%RH**	**20°C/45%RH**
Inulin 4 kDa-based SD with Primojel® incorporated	39 [a]	40 [a]
Inulin 4 kDa-based SD with Ac-Di-Sol® incorporated	68	67
PVP K30-based SD with Primojel® incorporated	33	37
PEG 20K-based SD with Primojel® incorporated	20	23

[a] Dissolution profiles of the tablets stored at 40°C/75%RH and 20°C/45%RH showed slightly faster than that of the tablets freshly prepared.

the mechanism by which the disintegration time is reduced by superdisintegrants is related to the swelling pressure and the hydration capacity of superdisintegrant, these properties should be considered. According to the study of Quadir and Kolter [18], Primojel® and Ac-Di-Sol® have higher swelling pressure and hydration capacity than Polyplasdone® XL and XL-10 (Table 5). Therefore, the inulin 4 kDa-based solid dispersion tablets in which Primojel® or Ac-Di-Sol® were incorporated disintegrated faster than those in which Polyplasdone® XL or XL-10 were incorporated. Furthermore, although the swelling pressure of Primojel® is lower than that of Ac-Di-Sol®, the dissolution rate of inulin 4 kDa-based solid dispersion tablets with either of the two superdisintegrants incorporated were comparable. This result might be ascribed to the higher hydration capacity of Primojel® compared to Ac-Di-Sol®.

The type of carrier also influenced dissolution behavior of the solid dispersion tablets (Fig. 6). Surprisingly, the disintegration time of HP-β-CD- or mannitol-based solid dispersion tablets were short but their drug releases were slow. After 2 h, the undissolved remnant of the tablets appeared to consist of fully crystalline fenofibrate. Possibly, HP-β-CD and mannitol dissolve so fast that even fast disintegration caused by the superdisintegrant could not prevent a high drug concentration in the near vicinity of the dissolving tablet resulting in uncontrolled recrystallization and the formation of large crystals which obviously dissolve slowly as also observed by van Drooge et al. [13]. In contrast, due to their polymeric nature, HP-β-CD and mannitol, inulin 4 kDa, PEG 20K and PVP K30 dissolve somewhat slower by which recrystallization of the drug was apparently prevented. Alternatively, it is also possible that during production of the HP-β-CD- and mannitol-based solid dispersions large drug crystals were formed in the carriers which obviously also dissolve slowly. Therefore, we can conclude that fast disintegration of the solid dispersion tablets is a prerequisite for fast dissolution but it does not guarantee it.

In summary, incorporation of a superdisintegrant in the drug containing solid dispersion is preferred over physical mixing of a superdisintegrant with the solid dispersion, the superdisintegrant Primojel® and Ac-Di-Sol® are preferred over

Table 5 Swelling pressures and hydration capacities of superdisintegrants (data taken from [18])

Superdisintegrants	Swelling pressure (kPa)	Hydration capacity (g water/ g polymer)
Primojel®	158	18.3
Ac-Di-Sol®	271	12.1
Polyplasdone® XL	110	5.8
Polyplasdone® XL-10	94	4.6

Polyplasdone® XL or XL-10 and the carriers inulin 4 kDa, PEG 20K and PVP K30 are preferred over HP-β-CD and mannitol. Therefore, the inulin 4 kDa-, PEG 20K- and PVP K30-based tablets in which Primojel® or Ac-Di-Sol® (only inulin 4 kDa-based tablets) was incorporated in the solid dispersion were selected for a storage stability study. After storage at 40°C/75%RH or 20°C/45%RH for 3 months, the inulin 4 kDa-based tablets showed fast dissolution indicating excellent storage stability (Fig. 8a-8b) although in the case of inulin 4 kDa-based solid dispersion tablets with Primojel® incorporated showed the dissimilar dissolution profile to tablets freshly prepared.

On the other hand, the dissolution behavior of the PEG 20K- and PVP K30-based tablets was deteriorated after storage indicating physical changes in time (Fig. 8c-8d). Possibly, despite of the solid nature of the carriers, there was some translational mobility in the carrier possible by which the drug particles aggregated in time. This is confirmed by Dordunoo et al. who reported that the particle size of triamterene or temazepam dispersed in PEGs increased during storage [19].

Because the marketed product Lipanthyl® contain 145 mg fenofibrate, the dissolution of 145 mg fenofibrate tablets prepared from inulin 4 kDa-based solid dispersions with Primojel® incorporated were compared to Lipanthyl® tablets (Fig. 7). Dissolution of tablets prepared from inulin 4 kDa-based solid dispersion with Primojel® incorporated was slightly slower than Lipanthyl® tablets. However, weight of this solid dispersion tablets was only 302 mg while weight of Lipanthyl® tablet was 640 mg. Therefore, to produce tablets weighing the same as Lipanthyl® tablets, 338 mg Avicel® PH-102 was physically mixed with inulin 4 kDa-based solid dispersion. The dissolution behavior of tablets prepared from this physical mixture was comparable to that of Lipanthyl® tablets.

In conclusion, incorporation of superdisintegrant in solid dispersions to prevent crystallization of drug during dissolution can be applied for some carriers. Type of carrier has profound effect on the dissolution behavior of solid dispersion in which superdisintegrant was incorporated. The fast dissolution behavior can be obtained by using the proper choices of carrier and superdisintegrant. In this study, fenofibrate tablets with a high drug load, excellent dissolution behavior and stability can be obtained when inulin 4 kDa-based solid dispersions are used in which Primojel® or Ac-Di-Sol® are incorporated.

ACKNOWLEDGMENTS

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CHAPTER 5

SURFACE-ACTIVE DERIVATIVE OF INULIN (INUTEC® SP1) IS A SUPERIOR CARRIER FOR SOLID DISPERSIONS WITH A HIGH DRUG LOAD

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5.1 ABSTRACT

The aim of this study was to compare the applicability of inulin, its surface active derivative (Inutec® SP1) and polyvinylpyrrolidone (PVP) as carriers in high drug load solid dispersions for improving the dissolution rate of a range of lipophilic drugs (diazepam, fenofibrate, ritonavir and efavirenz). The solid dispersions were prepared by spray freeze-drying. Scanning electron microscopy (SEM) showed that the obtained samples were highly porous spherical particles. Modulated differential scanning calorimetry (MDSC) showed that the drugs incorporated in these carriers were fully or partially amorphous. The solubility of the drugs in solutions of the different carriers was increased in the order: inulin 2.3 kDa < PVP K30 << Inutec® SP1. Dissolution behavior of solid dispersion tablets was evaluated. Inutec® SP1-based solid dispersion tablets showed the best performance followed by PVP- and inulin-based solid dispersion tablets. The superior dissolution behavior of the drugs from Inutec® SP1-based solid dispersions could be ascribed to its surface active nature. In addition, Inutec® SP1-based solid dispersion tablets gave good physical stability at 20°C/45%RH and 40°C/75%RH for 3 months.

5.2 INTRODUCTION

Increasing the dissolution rate of poorly-water soluble BCS class II drugs and thereby improving their bioavailability remains the challenging task for formulation scientists. Solid dispersions offer an interesting option to deal with this challenge. The method of production, the type of carrier [1-5], and formulation aspects such as incorporation of superdisintegrants [6], surfactants [7,8] or other excipients are only some of the parameters that may affect the performance of the solid dispersions.

In a previous study, we showed that dissolution of poorly-water soluble drugs from the inulin-based solid dispersion tablets was fast, except when the solid dispersions contained a high drug load. At high drug loads, the drug concentration in the near vicinity of the dissolving tablets was too high. The high drug concentration resulted in uncontrolled crystallization and the formation of large crystals which subsequently dissolved slowly [9]. Recently, an inulin derivative, Inutec® SP1, was described as stabilizer for emulsions [10]. Inutec® SP1 consists of a hydrophilic inulin backbone to which lipophilic alkyl side chains are covalently linked. The chemical structures of inulin and Inutec® SP1 are shown in Fig. 1. Inutec® SP1 can act as a surfactant due to the presence of both hydrophilic and lipophilic parts of the molecule. Due to its surface-active nature, it would be interesting to use Inutec® SP1 as a carrier for solid dispersions. Previously, the application of an inulin derivative for solid dispersions of itraconazole was described [11], however the carrier performance was not compared to other carriers nor was storage stability study of the solid dispersions at high drug loads investigated.

The aim of the present study was to investigate the applicability of Inutec® SP1 as a carrier for solid dispersions of various poorly-water soluble drugs at high drug loads, and to compare its behavior with native (non-surface active) inulin and polyvinylpyrrolidone (PVP). We speculate that compared to inulin-based solid dispersion tablets, higher drug loads can be applied in Inutec® SP1-based solid dispersion tablets without the occurrence of crystallization of the drug during dissolution. The high drug load in the boundary layer around the dissolving tablets (or particles) will not result in crystallization due to the surface-active nature of the inulin derivative. To investigate this mechanism, Inutec® SP1 was compared to native inulin as a carrier for solid dispersions. In addition, PVP was included in this study because it has been used as a successful carrier to produce amorphous solid dispersions [12-14]. The chemical structure of PVP is also shown in Fig. 1. Solid dispersions were prepared by spray freeze-drying using a water/tertiary butyl alcohol mixture as solvent. To investigate the versatility of Inutec® SP1 as a carrier for solid dispersions, four different poorly water-soluble drugs were used as model drugs, i.e. diazepam, fenofibrate, ritonavir and efavirenz. Storage stability of Inutec® SP1-based solid dispersions was also investigated.

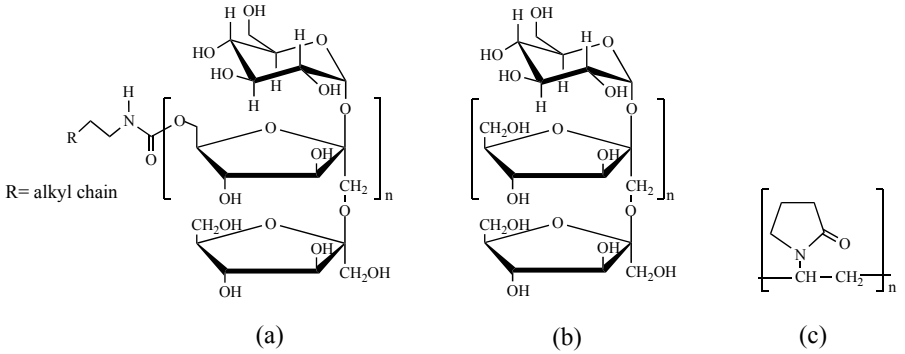

Figure 1 Chemical structures of (**a**) Inutec® SP1 (inulin lauryl carbamate), (**b**) native inulin and (**c**) PVP.

5.3 MATERIALS

The following materials were used as received: Inutec® SP1 (generously provided by BENEO-Orafti, Tienen, Belgium); inulin 2.3 kDa (Sensus, Roosendaal, The Netherlands); polyvinylpyrrolidone (PVP) K30 and diazepam (BUFA B.V., Uitgeest, The Netherlands); tertiary butyl alcohol (TBA) (Fluka Chemie GmbH, Steinheim, Germany); fenofibrate (Sigma-Aldrich Chemie GmbH, Steinheim, Germany); ritonavir and efavirenz (generously provided by the Government Pharmaceutical Organization, Bangkok, Thailand).

5.4 METHODS

5.4.1 Determination of surface tension

The surface tension of the aqueous solution at various Inutec® SP1, inulin 2.3 kDa, or PVP K30 concentrations was measured by a du Noüy ring-type tensiometer (Krüss Tensiometer K8, Hamburg, Germany) at 20 ± 1°C. The carrier solutions at concentrations of 0.0005 to 0.08% w/v were prepared in demineralized water. The tensiometer was calibrated with demineralized water before use (surface tension = 71.2 ± 0.2 mN/m). The surface tension measurement was performed in triplicate. The critical micelle concentration (CMC) was determined graphically from the slope change in the surface tension versus logarithm of the carrier concentration plot.

5.4.2 Determination of solubility

An excess amount of diazepam or fenofibrate was added to demineralized water, 5% w/v Inutec® SP1, inulin 2.3 kDa, or PVP K30 solutions. Efavirenz and ritonavir were treated similarly. However, because the solubility of these drugs are pH-dependent, 0.05 M phosphate buffer solution (PBS) pH 6.8 was used instead of demineralized water. Samples of the drugs in demineralized water or PBS pH 6.8 were used as controls.

All samples were stirred at room temperature (20°C) and were analyzed after 24 h (control experiment revealed that equilibrium was reached within 24 h). Samples were filtered through 0.2 μm filter prior to analysis and was then diluted with mobile phase to obtain the suitable concentration. The samples were analyzed by high performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Waters Model 510; Waters Associates, Milford, MA, USA), an autosampler (Waters Model 717 plus autosampler; Waters Associates), UV-detector (Model 783 Programmable Absorbance Detector; Applied biosystems, Foster City, CA, USA), a C18, 5 μm, 250 mm × 4.6 mm column (Nucleosil®; Macherey-Nagel GmbH&CO. KG, Düren, Germany).

For diazepam, the HPLC analysis was performed according to US Pharmacopeia (USP) [15] with some modifications, the mobile phase consisted of milli-Q water, acetronitrile and methanol (40:40:20, v/v/v), and at a flow rate of 1.0 mL/min. The detection wavelength was 254 nm. The retention time of diazepam was approximately 11.8 min. Linearity range was from 10 to 100 μg/mL ($r^2 \geq 0.999$).

For fenofibrate, the HPLC analysis was performed according to Granero et al. [16] with some modifications, the mobile phase consisted of acetronitrile and 0.02 M phosphoric acid solution (70:30, v/v), and at a flow rate of 1.2 mL/min. The detection wavelength was 286 nm. The retention time of fenofibrate was approximately 13.2 min. Linearity range was from 2 to 50 μg/mL ($r^2 \geq 0.999$).

For efavirenz, the HPLC analysis was performed according to Gadkari et al. [17] with some modifications, the mobile phase consisted of acetronitrile and 0.1 M ammonium acetate solution (60:40, v/v), and at a flow rate of 1.0 mL/min. The detection wavelength was 247 nm. The HPLC column was maintained at 30°C. The retention time of efavirenz was approximately 9.8 min. Linearity range was from 10 to 100 μg/mL ($r^2 \geq 0.999$).

For ritonavir, the HPLC analysis was performed according to Donato et al. [18] with some modifications, the mobile phase consisted of milli-Q water, acetronitrile and methanol (40:50:10, v/v/v), and at a flow rate of 1.0 mL/min. The detection wavelength was 210 nm. The retention time of ritonavir was approximately 11.2 min. Linearity range was from 10 to 100 μg/mL ($r^2 \geq 0.999$).

All measurements were performed in triplicate. The sample solutions were analyzed immediately after filtration.

5.4.3 Preparation of solid dispersions (SD)

Solid dispersions were prepared by spray freeze-drying as described by van Drooge et al. [19] with some modifications. The drugs were dissolved in pure TBA while the carriers were dissolved in demineralized water. Subsequently, the drug solution and carrier solution were mixed at volume ratio water/TBA of 4/6 which gave a clear and homogeneous solution during spraying process. The concentrations of both drugs and carriers in these mixtures are presented in Table 1.

Table 1 Composition of solutions for preparation of solid dispersions.

Drug[a] in water/TBA (mg/mL)	Carrier[b] in water/TBA (mg/mL)	Solid content in water/TBA (% w/v)	Drug load (% w/w)
2.60	10.40	1.3	20
3.90	9.10	1.3	30

[a] Diazepam, fenofibrate, ritonavir or efavirenz.
[b] Inutec® SP1, inulin 2.3 kDa or PVP K30.

The solutions (40 ml of each formulation) containing the drugs and carriers in the mixture of water/TBA were immediately after preparation sprayed into liquid nitrogen with a 0.5 mm two-fluid nozzle by Bűchi 190 mini spray dryer (Bűchi, Flawil, Switzerland). The liquid feed rate was 15 mL/min and the atomizing-air flow was 500 L_n/h (500 liters of air at 1 atm and 0°C per hour). The outlet of nozzle was positioned about 10 cm above liquid nitrogen and the jacket of the nozzle was circulated with hot water (about 90°C) to prevent the solutions from freezing during spraying. After evaporation of the liquid nitrogen, the samples were transferred into Christ Model Epsilon 2-4 freeze dryer (Salm and Kipp, Breukelen, The Netherlands). Freeze drying was performed according to a two-step procedure. First, the pressure was set at 0.220 mbar and the shelf temperature at -35°C for one day. Subsequently, the pressure was reduced to 0.05 mbar, while the shelf temperature was gradually raised to 20°C. This condition was maintained for another day. During the whole cycle, the condenser temperature was -85°C. After freeze drying the samples were placed in a vacuum desiccator over silica gel at room temperature for at least one day before further experiments.

5.4.4 Preparation of physical mixtures (PM)

The drugs and the carriers at the corresponding ratios of solid dispersions were gently mixed by using a mortar and a spatula. The samples were placed in a vacuum desiccator over silica gel at room temperature.

5.4.5 Tableting

Samples were taken out from a vacuum desiccator and subsequently compressed to tablets using an ESH compaction apparatus (Hydro Mooi, Appingedam, The Netherlands). The powders composed of diazepam and carrier were compressed to a tablet of 50 mg with a diameter of 7 mm. The maximum compression force of 3 kN was reached in 3 s. The powders composed of fenofibrate, ritonavir or efavirenz and carrier were compressed to a tablet of 100 mg with a diameter of 9 mm. The maximum compression force of 5 kN was reached in 5 s. The tablets were stored for at least one day in a vacuum desiccator over silica gel at room temperature before analysis.

5.4.6 Modulated differential scanning calorimetry (MDSC)

A modulated differential scanning calorimeter (MDSC Q2000, TA Instruments, Ghent, Belgium) was used to characterize the physical state of pure drugs and carriers as received, and solid dispersions. About 2-4 mg of samples was weighed in a standard aluminium open pan. The empty pan of the same type was used as a reference. Samples containing fenofibrate were heated from -50 to 200°C and samples containing diazepam, ritonavir or efavirenz were heated from 10 to 200°C. All samples were run with a heating rate of 2°C/min (modulation amplitude 0.318°C, modulation period 60 s, resulting in heating-only conditions) while being purged with pure nitrogen gas. Calibrations of temperature and heat flow were carried out with indium. The inflection point of the transition was taken as the glass transition (T_g). The sharp endothermal peak of the thermogram was detected as the melting point (T_m). Melting and quench-cooling method was used for preparing pure amorphous drugs. Pure drugs were heated to about 2-3°C above their melting points. After 5 min, the samples were cooled down to -50°C with a cooling rate of 20°C/min and then were run by MDSC method as described above. In addition, the percent relative crystallinity of drug was calculated using the following formula.

$$\text{Relative crystallinity (\%)} = \frac{\Delta Hf_{SD} \times 100}{\Delta Hf_d \times w_d}$$

where ΔHf_{SD} is the enthalpy of fusion of drug in solid dispersions, ΔHf_d is the enthalpy of fusion of pure drug and w_d is weight fraction of drug in solid dispersions.

All measurements were performed at least in duplicate.

5.4.7 Scanning electron microscopy (SEM)

The morphology of samples was examined with a scanning electron microscope (JEOL JSM 6301F; JEOL Ltd., Tokyo, Japan) operating at 5 kV. The samples were mounted on a metal stub with double-sided sticky carbon tape and coated with 80 mm of gold/palladium in a Balzers 120B sputtering device (Balzers UNION, Balzers, Liechtenstein).

5.4.8 Determination of water vapor sorption

The hygroscopicity of samples was measured by using a gravimetric sorption analyzer (DVS-1000 Water Sorption Instrument, Surface Measurement System Limited, London, UK). About 10 mg of samples was initially dried by exposing them to 25°C/0% relative humidity (RH). When the change of sample mass was less than 0.00050% w/w per min during a 10 min-period, equilibrium was assumed and the humidity was then changed to 30% RH again until the equilibrium was obtained. The amount of water absorbed was expressed as the mass percentage of water relative to the mass of dried sample. All measurements were conducted at least in duplicate.

5.4.9 Dissolution experiments

Dissolution of tablets was carried out by using a USP dissolution apparatus II (Rowa Techniek, Leiderdorp, The Netherlands) with a paddle at 100 rpm and 37°C under sink conditions. One liter of demineralized water was used for diazepam and one liter of demineralized water containing 0.5% w/v sodium lauryl sulfate (SLS) was used for fenofibrate, ritonavir and efavirenz. The dissolution medium was continuously circulated through UV-spectrophotometer flow cells (Model Ultraspec III; Pharmacia LKB, Uppsala, Sweden) at 20 mL/min using a peristaltic pump (Ismatec, Zurich, Switzerland). The samples were filtered through 0.35 μm filter prior to analysis. Concentration of the drug in dissolution medium was measured every 2 min for 2 h at a wavelength of 230 nm for diazepam, 290 nm for fenofibrate, 240 nm for ritonavir and 247 nm for efavirenz. All measurements were conducted in triplicate.

5.4.10 Stability study

Solid dispersion tablets were stored under closed vial conditions in climate chambers at 20°C/45% RH and 40°C/75% RH for 3 months. The dissolution behavior of these tablets was then evaluated in triplicate.

5.5 RESULTS

5.5.1 Surface tension studies

The surface tensions of Inutec® SP1, inulin 2.3 kDa and PVP K30 aqueous solutions at different concentrations are presented in Fig. 2. With increasing concentration of

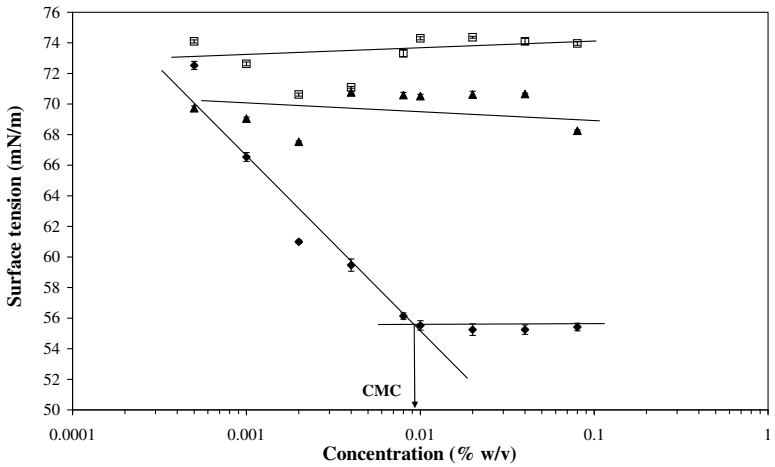

Figure 2 Surface tension of different carriers in aqueous solution at 20°C (♦: Inutec® SP1, □: inulin 2.3 kDa and ▲: PVP K30).

Inutec® SP1, first the surface tension decreased from 73 mN/m to 55 mN/m and then remained constant at higher concentrations. The concentration above which the surface tension remained the same, the CMC, was 0.009% w/v. From these measurements, it is clear that Inutec® SP1 can form micelles in aqueous solution. On the other hand, the surface tension of aqueous inulin 2.3 kDa and PVP K30 solutions did not show a slope change by increasing the concentration of carrier, indicating that these carriers are not surface-active compounds. The surface tension of aqueous inulin 2.3 kDa solutions was about 71-74 mN/m which was significantly different ($p < 0.05$) from that of demineralized water (71.2 ± 0.2 mN/m). However, the curve of the surface tension as a function of the inulin 2.3 kDa concentration did not have the shape which is typical for a surfactant such as Inutec® SP1. The surface tension of aqueous PVP K30 solutions was about 68-70 mN/m which was not significantly different from that of demineralized water ($p > 0.05$).

5.5.2 Solubility studies

Table 2 shows the solubility of diazepam, fenofibrate, ritonavir and efavirenz in different solutions at room temperature. The solubilities of diazepam and fenofibrate in demineralized water, and efavirenz and ritonavir in PBS (pH 6.8) are lower than the values reported in previous publication [20-24] most likely because we determined the solubility at 20°C instead of 37°C. A higher temperature usually results in an increased solubility of drugs [25]. The solubility of all four drugs in 5% w/v Inutec® SP1 solution was strongly increased. On the other hand, in 5% w/v inulin 2.3 kDa solution, the solubility of the drugs tested did not increase as compared to the solubility in demineralized water or in the buffer solutions. Furthermore, in 5% w/v PVP K30 solution, the solubility of these drugs was higher than that in demineralized water, but substantially lower than in 5% w/v Inutec® SP1 solution. Patel and Vavia also reported that fenofibrate solubility was increased in a PVP solution [26].

Table 2 Solubility of diazepam, fenofibrate, ritonavir and efavirenz in demineralized water or phosphate buffer solution (PBS) pH 6.8, demineralized water or PBS pH 6.8 with 5% w/v carrier solutions at 20°C (n=3, mean ± s.d.).

Solutions	**Solubility (mg/L)**			
	Diazepam[a]	**Fenofibrate[a]**	**Ritonavir[b]**	**Efavirenz[b]**
Demineralized water or PBS pH 6.8	51.0 ± 1.3	0.039 ± 0.004	0.90 ± 0.07	3.9 ± 0.9
Inutec® SP1	1003.9 ± 7.6*	106.3 ± 1.6*	726.1 ± 6.1*	1174.1 ± 5.3*
Inulin 2.3 kDa	49.3 ± 0.8	0.037 ± 0.001	0.76 ± 0.01	3.1 ± 0.7
PVP K30	71.8 ± 0.8*	0.087 ± 0.010*	2.05 ± 0.36*	10.1 ± 1.7*

[a] Solubility of diazepam and fenofibrate was tested in demineralized water.
[b] Solubility of ritonavir and efavirenz was tested in 0.05 M phosphate buffer pH 6.8.
* $p < 0.05$ (Significant difference as compared to demineralized water or PBS pH 6.8).

Table 3 Melting point (T_m), enthalpy of fusion (ΔHf) and glass transition temperature (T_g) of pure substances (n = 2-3, mean ± s.d.).

Samples	T_m (°C)	ΔHf (J/g)	T_g (°C)
Diazepam	131.4 ± 0.1	95.3 ± 1.9	46.8 ± 0.2
Fenofibrate	80.6 ± 0.2	98.3 ± 2.4	-19.6 ± 0.2
Ritonavir	121.5 ± 0.2	70.6 ± 1.6	50.2 ± 0.5
Efavirenz	137.7 ± 0.1	47.7 ± 0.8	37.3 ± 0.2
Inutec® SP1	-	-	144.8 ± 1.2
Inulin 2.3 kDa	-	-	142.1 ± 0.5
PVP K30	-	-	163.9 ± 2.3

Table 4 Glass transition temperature (T_g) of spray freeze-dried solid dispersions (n = 2-3, mean ± s.d.).

Samples	T_g (°C)		
	Inutec® SP1	Inulin 2.3 kDa	PVP K30
20% w/w drug load			
Diazepam	140.3 ± 1.9	141.5 ± 1.8	128.7 ± 0.1
Fenofibrate[a]	144.1 ± 1.0	143.3 ± 0.9	112.4 ± 0.7
	T_m = 76.4 ± 0.1 % Cryst. = 16.8 ± 2.2	T_m = 76.1 ± 0.3 % Cryst. = 14.6 ± 2.9	T_m = 78.4 ± 0.1 % Cryst. = 2.3 ± 0.6
Ritonavir	141.7 ± 0.1	142.5 ± 1.6	132.4 ± 2.3
Efavirenz	140.9 ± 0.7	138.9 ± 1.1	138.3 ± 0.3
30% w/w drug load			
Diazepam	138.6 ± 0.6	138.3 ± 1.2	100.9 ± 0.7
Fenofibrate[a]	142.6 ± 0.7	144.9 ± 1.0	144.8 ± 2.1
	T_m = 74.7 ± 0.4 % Cryst. = 25.0 ± 0.5	T_m = 74.2 ± 0.2 % Cryst. = 24.2 ± 1.2	T_m = 77.7 ± 0.3 % Cryst. = 3.1 ± 0.9
Ritonavir	140.1 ± 0.9	139.0 ± 0.7	119.7 ± 0.9
Efavirenz	138.6 ± 0.1	141.5 ± 1.0	123.4 ± 0.6

[a] Results presented the melting point (T_m) of fenofibrate and % relative crystallinity (% Cryst.) in addition to the T_g.

5.5.3 MDSC studies

The T_ms and T_gs of pure diazepam, fenofibrate, ritonavir and efavirenz, and T_gs of pure Inutec® SP1, inulin 2.3 kDa and PVP K30 are presented in Table 3. Furthermore, Table 4 summarizes the T_gs and T_ms detected from thermograms of all solid dispersions.

The thermal events of Inutec® SP1-based solid dispersions in which diazepam, ritonavir, efavirenz or fenofibrate was incorporated at drug loads of 20% and 30% w/w

gave the same trends as the corresponding inulin 2.3 kDa-based solid dispersions. The thermograms showed one T_g which was close to the T_g of the pure carrier and lack the $T_g s$ of drugs in case of diazepam, ritonavir and efavirenz. This indicates that the drugs were homogeneously distributed in the carriers [27].

For fenofibrate with 20% and 30% w/w drug loads incorporated in Inutec® SP1 or inulin 2.3 kDa-based solid dispersions, the thermograms showed a melting peak and a T_g which were close to the melting peak of fenofibrate and the T_g of pure carrier, respectively. These results indicate that fenofibrate was partially crystalline and partially amorphous incorporated in the carriers. For Inutec® SP1-based solid dispersions with 20% and 30% w/w drug loads, the relative crystallinity of fenofibrate was 16.8% and 25.0%, respectively. In case of inulin 2.3 kDa-based solid dispersions, the relative crystallinity of fenofibrate was 14.6% when the drug load was 20% w/w and 24.2% when the drug load was 30% w/w.

In case of PVP K30-based solid dispersions with diazepam, ritonavir or efavirenz at drug loads of 20% and 30% w/w, the thermograms showed one T_g in between the T_g of the pure drug and PVP K30, indicating that the drugs were homogeneous distributed in the carrier. The thermograms of fenofibrate at drug loads of 20% and 30% w/w in PVP K30-based solid dispersions showed a melting peak of the drug and one T_g which was in between the $T_g s$ of the drug and carrier. This indicates that the drug was partially crystalline and partially amorphous. The relative crystallinity of fenofibrate was 2.3% when the drug load was 20% w/w and 3.1% when the drug load was 30% w/w in PVP K30-based solid dispersions.

5.5.4 SEM studies

Spray freeze-dried powders with a drug load of 30% w/w in Inutec® SP1, inulin 2.3 kDa, PVP K30 carriers were subjected to SEM examination. As can be seen in Fig. 3a-c, the particle size and morphology of solid dispersion powders of efavirenz incorporated in different carriers was similar for all carriers. The solid dispersion powders were highly porous (Fig. 3d-f). The particle size and morphology of the solid dispersion powders with the three other drugs incorporated were similar.

5.5.5 Water vapor sorption studies

The amount of water absorbed at 25°C/30%RH by spray freeze-dried powders composed of pure Inutec® SP1, inulin 2.3 kDa and PVP K30 or by solid dispersions containing 30% w/w drug load in the carriers tested are presented in Table 5. As expected the amount of water absorbed by the solid dispersions was substantially lower than that by the pure carrier. Moreover, to compare with the solid dispersions, the amount of water absorbed by the corresponding physical mixtures containing the same drug load in the carriers tested is shown in Table 6. Compared to the solid dispersions, the amount of water absorbed by physical mixtures was slightly increased for Inutec® SP1-, similar for inulin 2.3 kDa- and substantially increased for PVP K30-based mixtures.

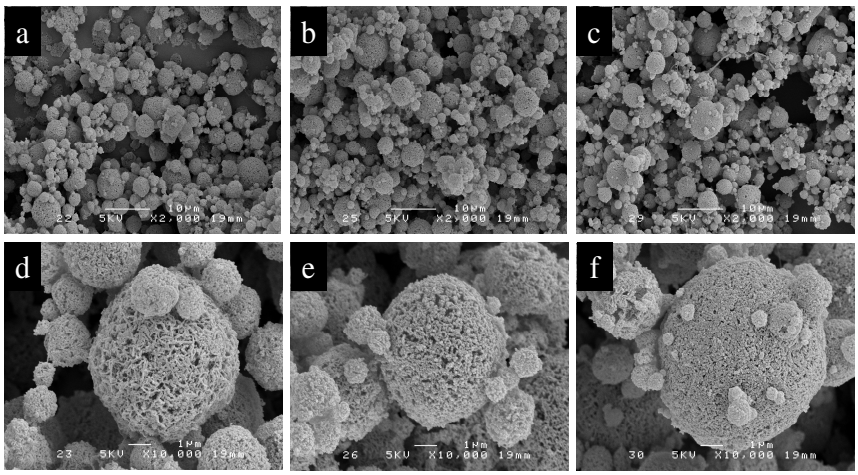

Figure 3 SEM pictures of spray freeze-dried solid dispersions with efavirenz incorporated at a drug load of 30%w/w in different carriers: (**a**) Inutec® SP1 (magnification 2000X), (**b**) inulin 2.3 kDa (magnification 2000X), (**c**) PVP K30 (magnification 2000X), (**d**) Inutec® SP1 (magnification 10000X), (**e**) inulin 2.3 kDa (magnification 10000X) and (**f**) PVP K30 (magnification 10000X).

Table 5 The amount of water absorbed at 25°C/30%RH by spray freeze-dried samples of pure carriers and by solid dispersions containing 30% w/w drug load in carriers (n = 2-3, mean ± s.d.).

Samples	Pure carrier	Diazepam	Fenofibrate	Ritonavir	Efavirenz	Average value[a]
Inutec® SP1	5.18 ± 0.23	3.52 ± 0.14	3.53 ± 0.35	3.81 ± 0.02	3.79 ± 0.12	3.66 ± 0.21
Inulin 2.3 kDa	5.75 ± 0.37	3.96 ± 0.07	4.10 ± 0.01	4.43 ± 0.18	4.23 ± 0.05	4.18 ± 0.20
PVP K30	10.42 ± 0.58	5.17 ± 0.14	5.59 ± 0.06	5.89 ± 0.11	4.30 ± 0.18	5.24 ± 0.65

[a] The average value was calculated from the results of four drugs tested.

Table 6 The amount of water absorbed at 25°C/30%RH by physical mixtures containing 30% w/w drug load in carriers (n = 2-3, mean ± s.d.).

Samples	Diazepam	Fenofibrate	Ritonavir	Efavirenz	Average value[a]
Inutec® SP1	4.10 ± 0.04	4.19 ± 0.02	4.11 ± 0.01	4.23 ± 0.08	4.16 ± 0.07
Inulin 2.3 kDa	4.07 ± 0.04	4.06 ± 0.03	4.14 ± 0.00	4.20 ± 0.08	4.12 ± 0.07
PVP K30	7.29 ± 0.08	7.28 ± 0.11	7.41 ± 0.09	7.31 ± 0.22	7.32 ± 0.12

[a] The average value was calculated from the results of four drugs tested.

5.5.6 Dissolution studies

5.5.6.1 Effect of drug load on dissolution of Inutec® SP1-, inulin 2.3 kDa- or PVP K30-based solid dispersion tablets

The times at which 80% of drug was dissolved ($t_{80\%}$) from all solid dispersion tablets with various carriers and drugs at 20% and 30% w/w drug loads are presented in Fig. 4. In the case of 20% w/w drug load in Inutec® SP1 solid dispersions, the dissolution of all four drugs was fast, the $t_{80\%}$ values were less than 20 min. Also, when the drug load was increased to 30% w/w, dissolution remained fast ($t_{80\%}$ < 30 min).

For inulin 2.3 kDa-based solid dispersion tablets containing 20% and 30% w/w diazepam, the dissolution of diazepam was slow ($t_{80\%}$ > 2 h). For fenofibrate, efavirenz and ritonavir, the $t_{80\%}$ values of solid dispersion tablets at 20% w/w drug load in inulin 2.3 kDa was less than 20 min. However, when the drug load of fenofibrate, efavirenz and ritonavir was increased to 30% w/w, the $t_{80\%}$ values of these solid dispersion tablets were more than 45 min. Lastly, when using PVP K30 as carrier, at 20% w/w diazepam, fenofibrate and ritonavir, the dissolution of the drugs was also fast ($t_{80\%}$ < 30 min). For 20% w/w efavirenz in PVP K30, $t_{80\%}$ was about 37 min. However, when the drug load was increased to 30% w/w, the dissolution of all four drugs became slow ($t_{80\%}$ > 45 min).

5.5.6.2 Effect of storage conditions on dissolution of drugs containing in Inutec® SP1-based solid dispersion tablets

According to the results described above, incorporation of the drugs at the 30% w/w drug load level gave the fastest dissolution when Inutec® SP1 was used as carrier. Therefore, the storage stability of these formulations was investigated. The tablets were stored at 20°C/45%RH and 40°C/75%RH for 3 months after which the dissolution

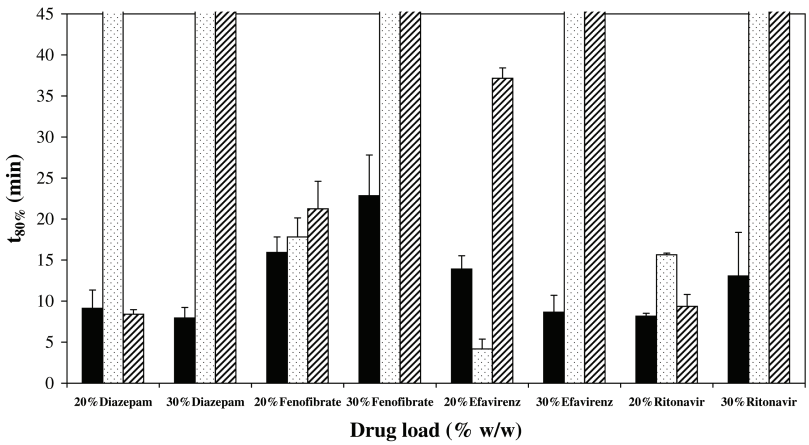

Figure 4 Effect of drug loads on time at which 80% of drug was dissolved ($t_{80\%}$) from different carrier-based solid dispersion tablets (close bar: Inutec® SP1, dot bar: inulin 2.3 kDa and striped bar: PVP K30) (data shown as mean value with standard deviation error bar).

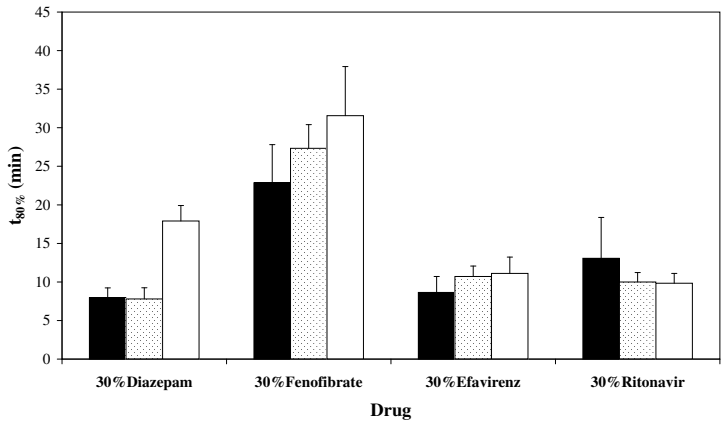

Figure 5 Effect of different storage conditions on time at which 80% of drug was dissolved ($t_{80\%}$) from Inutec® SP1-based solid dispersion tablets containing 30% w/w drug load (close bar: freshly prepared, dot bar: stored at 20°C/45%RH for 3 months, and open bar: stored at 40°C/75%RH for 3 months) (data shown as mean value with standard deviation error bar).

behavior was determined and compared to that of freshly prepared tablets. The $t_{80\%}$ values of these solid dispersion tablets are presented in Fig. 5.

Although, the $t_{80\%}$ value of Inutec® SP1-based solid dispersion tablets containing diazepam stored at 40°C/75%RH was increased in comparison with that of the freshly prepared tablets or tablets stored at 20°C/45%RH, the dissolution of the solid dispersion tablets stored at 40°C/75%RH was still fast. The $t_{80\%}$ values of Inutec® SP1-based solid dispersion tablets containing diazepam, ritonavir and efavirenz at 20°C/45%RH and 40°C/75%RH remained less than 20 min. For fenofibrate in Inutec® SP1-based solid dispersion tablets, the $t_{80\%}$ values of these solid dispersion tablets at 20°C/45%RH and 40°C/75%RH were about 30-35 min. The $t_{80\%}$ values of the solid dispersion tablets at both the storage conditions were close to that of freshly prepared tablets.

During storage the drugs could crystallize and/or aggregate which would affect the dissolution behavior. Since before and after storage, the dissolution profiles were similar, we can conclude that the Inutec® SP1-based solid dispersion tablets are physically stable for 3 months at 20°C/45% RH and 40°C/75%RH.

5.6 DISCUSSION

This study clearly shows that Inutec® SP1 is an excellent carrier for high drug load solid dispersions of highly lipophilic drugs. The versatility of Inutec® SP1 as a carrier for solid dispersion to improve the dissolution of these drugs is shown by the fast dissolution of four different model drugs incorporated at the high drug load of 30% w/w.

The applicability of Inutec® SP1, as carrier in solid dispersions was compared with inulin 2.3 kDa and PVP K30. Inulin 2.3 kDa was used as a control because the T_gs of

inulin with a molecular weight of 2.3 kDa and Inutec® SP1 are comparable (Table 3). Since PVP K30 is a frequently used as a carrier in solid dispersions that also interacts with drugs, we considered that it was interesting to compare with this material as well. Diazepam, fenofibrate, efavirenz and ritonavir were chosen as model drugs because they are all poorly water-soluble drugs.

Solid dispersions with diazepam, ritonavir or efavirenz incorporated at 20% and 30% w/w drug loads in Inutec® SP1, inulin 2.3 kDa or PVP K30 were homogeneous amorphous dispersions as shown by the occurrence of one single T_g (Table 4). Interestingly, for diazepam incorporated in inulin-based solid dispersions, spray freeze-drying resulted in dispersions in which the drug up to 30% w/w was homogeneously dispersed, whereas the solid dispersions with diazepam loading up to only 10% w/w produced by freeze drying gave homogeneously solid dispersions [27]. This indicates that spray freeze-drying method can be used for incorporating drugs at a high drug load in homogeneous amorphous solid dispersions. In contrast to diazepam, ritonavir or efavirenz, solid dispersions in which fenofibrate was incorporated in the same carriers at the same drug loads showed partial phase separation as a small amount of fenofibrate was crystalline. The partial phase separation of fenofibrate in solid dispersions is most likely due to the low T_g of fenofibrate (-19.6°C), resulting in crystallization during the freeze-drying process.

The solubility of all four drugs was strongly increased in 5% w/v Inutec® SP1 solution (Table 2). This can be ascribed to the fact that the concentration of 5% w/v Inutec® SP1 in demineralized water is higher than the CMC (0.009% w/v) (Fig. 2). It can be assumed that due to hydrophobic interaction, the lipophilic drug will be incorporated in the core of the micelles. A smaller amount of water was absorbed by the spray freeze-dried solid dispersions composed of pure Inutec® SP1 than by the spray freeze-dried solid dispersions composed of pure inulin 2.3 kDa although not significantly different ($p > 0.05$). Obviously, this can be ascribed to the fact that hydrophobic side chains of Inutec® SP1 absorb substantially less water than the hydrophilic backbone of the molecule. Furthermore, as shown in Table 5 and 6, the amount of water absorbed by Inutec® SP1-based solid dispersions at a drug load of 30% w/w was significantly decreased in comparison with that by the corresponding physical mixtures ($p < 0.05$). The relative percentage decrease in the amount of water absorbed was about 11.9%.

In inulin 2.3 kDa solution (5% w/v), the solubility of diazepam, fenofibrate, ritonavir and efavirenz was not increased in comparison with that in demineralized water (Table 2). This indicates that these drugs do not interact with inulin 2.3 kDa. In addition, as can been seen in Table 5 and 6, the amount of water absorbed at 25°C/30%RH by inulin 2.3 kDa-based solid dispersions and that by the corresponding physical mixtures was similar, also indicating the absence of drug-carrier interaction in inulin 2.3 kDa-based solid dispersions.

In PVP K30 solutions (5% w/v), the solubility of diazepam, fenofibrate, ritonavir and efavirenz was increased (Table 2). These results indicate that the drugs do interact with

PVP. Furthermore, the amount of water absorbed at 25°C/30%RH by PVP K30-based solid dispersions was significantly decreased as compared to that by the corresponding physical mixtures ($p < 0.05$) (Table 5 and 6). The relative percentage decrease in the amount of water absorbed was about 28.5%. This result is consistent with previous studies [27,28]. PVP K30 in the solid dispersions was hydrophobized by the drugs which confirms the drug-carrier interaction. Both Inutec® SP1- and PVP K30-based solid dispersions with 30% w/w drug load showed significantly decrease in the amount of water absorbed as compared to the corresponding physical mixtures, indicating drug-carrier interaction. However, the relative percentage decrease in the amount of water absorbed by the PVP K30-based solid dispersions (28.5%) was much larger than that by Inutec® SP1-based solid dispersions (11.9%). This implied that the hydrophilic inulin backbone was much less hydrophobized by the drug as compared to PVP K30. However, the aqueous solubilities of the drugs in Inutec® SP1 solutions were much higher than that in PVP K30 solutions indicating a much stronger interaction between Inutec® SP1 and the drugs than between PVP K30 and the drugs. Consequently, it can be concluded that indeed the drugs predominantly interact with the hydrophobic side chains of Inutec® SP1 molecule.

In conclusion, the solid dispersions of Inutec® SP1 or PVP K30 showed drug-carrier interaction. On the other hand, the drug-carrier interaction was absent in the solid dispersions in which the drugs were incorporated in inulin 2.3 kDa.

With Inutec® SP1 as carrier, rapid dissolution was achieved for all drugs tested and at both drug loads. In contrast, with inulin 2.3 kDa carrier, drug dissolution was slower especially at the high drug load. Furthermore, at the lower drug load there was a strong effect of the drugs tested on the dissolution behavior. The superior dissolution behavior of Inutec® SP1-based solid dispersion tablets at high drug loads compared to inulin 2.3 kDa- or PVP K30-based solid dispersion tablets can be explained by the differences in saturation concentration of the drugs in different carrier solutions (Table 2). As the solubility of all four drugs in Inutec® SP1 solution was strongly increased, the saturation concentration in the boundary layer around the dissolving tablet will also be increased. Therefore, the driving forces for drug dissolution will be increased, while the risk of drug crystallization will be reduced. Consequently, at high drug loads, the dissolution behavior of the drugs was still excellent. On the other hand, in inulin 2.3 kDa solution, the saturation concentration of all four drugs was not increased. Thus, crystallization of the drug in the vicinity of dissolving tablets occurred when the drug was incorporated at high drug loads. In PVP K30 solutions, the saturation concentration of all four drugs was increased but substantially less than that in the Inutec® SP1 solution. Therefore, the dissolution behavior of the drugs from PVP K30-based solid dispersions was much poorer than that from Inutec® SP1-based solid dispersions.

As the freshly prepared Inutec® SP1-based solid dispersion tablets gave excellent dissolution behavior, the storage stability at 20°C/45%RH and 40°C/75%RH for

3 months of these tablets was examined. The dissolution behavior of these solid dispersion tablets even at high drug load remained fast (Fig. 5).

In summary, Inutec® SP1 with its surface-active properties is a promising carrier for solid dispersions with a high drug load to improve the dissolution behavior of lipophilic drugs.

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CHAPTER 6

PREPARATION AND PHYSICOCHEMICAL EVALUATION OF A NEW TACROLIMUS TABLET FORMULATION FOR SUBLINGUAL ADMINISTRATION

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6.1 ABSTRACT

The aim of this study was to develop a new sublingual tablet formulation containing 1 mg tacrolimus. First, solid dispersions containing tacrolimus (2.5%, 5% and 10% w/w) incorporated in Ac-Di-Sol® and carriers (inulin 1.8 kDa and 4 kDa, and polyvinylpyrrolidone (PVP) K30) were prepared by freeze drying. Subsequently, a tablet formulation composed of a mixture of the solid dispersions, Ac-Di-Sol®, mannitol, Avicel® PH-101 and sodium stearyl fumarate was optimized concerning drug load in the solid dispersions and the type of carrier. Tablet weight was kept constant at 75 mg by adjusting the amount of Avicel® PH-101. X-ray powder diffraction (XRPD) results indicated the absence of crystalline drug. This was confirmed by the scanning electron microscopy (SEM) results. These results suggest that tacrolimus incorporated in any all solid dispersions was fully amorphous. Dissolution of the tablets containing solid dispersions with a low drug load highly depended on the type of carrier and increased in the order: PVP K30 < inulin 4 kDa < inulin 1.8 kDa. Solid dispersions with a drug load of 10% w/w incorporated in the carriers yielded optimal formulations. In addition, the physicochemical characteristics and the dissolution behavior of the tablet formulation containing inulin 1.8 kDa-based solid dispersions with a drug load of 10% w/w did not change after storage at 20°C/45%RH for 6 months indicating excellent stability.

6.2 INTRODUCTION

Tacrolimus is a biopharmaceutics classification system (BCS) class II drug. It has a low aqueous solubility and a high permeability [1]. The drug has been used as an immunosuppressant in patients to prevent rejection after organ transplantation [2-4]. Tacrolimus capsules for oral administration is one of available marketed products. Pharmacokinetics studies in transplant patients have shown that oral bioavailability of tacrolimus was low and highly variable (6-43%, mean 20%) [5]. The major reasons for the low oral bioavailability are a low aqueous solubility of the drug and the first pass metabolism in liver. To overcome low bioavailability, various approaches to increase the drug dissolution rate and alternative dosage forms to avoid extensive metabolism in liver have been investigated [6].

Application of solid dispersions which consist of a hydrophilic carrier in which a lipophilic drug is incorporated is a proven method to increase the dissolution rate of the drug. Many studies on solid dispersions have proved that the bioavailability of lipophilic drugs was significantly enhanced by this technology [7-10]. However, in case of tacrolimus, the solid dispersion technique could solve the poor aqueous solubility problem but not the first pass effect problem. Therefore, the solid dispersion technique combined with an alternative route of administration i.e. sublingual tablets may further improve the bioavailability of tacrolimus. A sublingual tablet is a dosage form aiming for systemic drug absorption through the highly vascularized oral mucosa. Thereby tacrolimus enters directly into the systemic circulation and thus circumvents first pass metabolism in the liver [11]. By opening the marketed capsules and placing the powder content under the patient's tongue, tacrolimus may be administered via the sublingual route [12]. However, this approach bears the risk of subtherapeutic dosing caused by loss of the powder when opening the capsule. To our knowledge, formulation of tacrolimus sublingual tablets has not been reported.

The aims of the present study were to develop a tacrolimus sublingual tablet formulation in which tacrolimus was processed as solid dispersions and to investigate its dissolution behavior. In addition, the storage stability of the tablets was studied for future clinical trials. Inulin 1.8 kDa and 4 kDa, and polyvinylpyrrolidone (PVP) K30 were used as carriers for the solid dispersions.

6.3 MATERIALS

The following materials were purchased from various suppliers and were used as received: tacrolimus (as monohydrate) from Concord Biotech Limited, Ahmedabad, India, inulin 1.8 kDa and 4 kDa from Sensus, Roosendaal, The Netherlands), polyvinylpyrrolidone (PVP K30) from BUFA B.V., Uitgeest, The Netherlands, croscarmellose sodium (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH-101) from FMC Biopolymer, Philadelphia, USA, mannitol (Pearlitol® SD) from Roquette, Lestrem, France, sodium

stearyl fumarate (Pruv®) from JRS PHARMA GmbH, Rosenberg, Germany, and tertiary butyl alcohol (TBA) from Fluka Chemie GmbH, Steinheim, Germany.

6.4 METHODS

6.4.1 Preparation of solid dispersions (SD)

The drug was dissolved in pure TBA. Inulin 1.8 kDa, 4 kDa or PVP K30 together with Ac-Di-Sol® were dissolved in demineralized water. The two solutions were mixed at a water/TBA ratio of 6/4 (v/v). To prepare different drug loads of 2.5%, 5% and 10% w/w, drug and carrier concentrations were appropriately adjusted while the concentration of Ac-Di-Sol® was constant at 4% w/w as shown in Table 1. After mixing, the vials containing the sample were immediately immersed into liquid nitrogen. Subsequently, the vials were transferred into a freeze dryer (Salm and Kipp, Breukelen, The Netherlands). The typical lyophilization cycle was performed in two steps according to a process as described by van Drooge et al. [13]. First, the pressure was set at 0.220 mbar and the shelf temperature at -35°C for one day. Subsequently, the pressure was reduced to 0.05 mbar, while the shelf temperature was gradually raised to 20°C. This condition was maintained for another day. During the whole cycle the condenser temperature was -85°C. After freeze drying the samples were placed in a vacuum desiccator over silica gel at room temperature for at least one day.

To prepare placebo samples, pure TBA was used instead of a solution of drug in TBA. The other steps were carried out in the same way as described for the solid dispersions.

Table 1 Composition of solutions for preparation of solid dispersions.

Tacrolimus monohydrate in water/TBA (mg/mL)	Carrier[a] in water/TBA (mg/mL)	Ac-Di-Sol® in water/TBA (mg/mL)	Solid content in water/TBA (% w/v)	Drug load (% w/w)
0.64	23.38	1.00	2.5	2.5
1.28	22.75	1.00	2.5	5
2.56	21.50	1.00	2.5	10

[a] Inulin 1.8 kDa and 4 kDa, and PVP K30.

6.4.2 X-ray powder diffraction (XRPD)

Solid dispersions and corresponding physical mixtures were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, The Netherlands) with a copper anode (Cu Kα radiation, λ= 0.15405 nm, 40 kV, 40 mA). The diffraction pattern was measured with a step size of 0.008° and a dwell time of 45 s at each step between 4-50 2θ at ambient temperature.

6.4.3 Scanning electron microscopy (SEM)

The morphology of samples was examined with a scanning electron microscope (JEOL JSM 6301F; JOEL Ltd., Tokyo, Japan) operating at 5 kV. The samples were mounted on a metal stub with double-sided sticky carbon tape and coated with 80 mm of gold/palladium in a Balzers 120B sputtering device (Balzers UNION, Balzers, Liechtenstein).

6.4.4 Preparation of sublingual tablets containing tacrolimus solid dispersions (SD)

Sublingual tablets were prepared with a tacrolimus content of 1 mg. The formulations of the sublingual tablets are presented in Table 2. Freeze-dried powder consisting of tacrolimus, Ac-Di-Sol® and carrier was sieved through a stainless steel sieve #30 (sieve size: 0.6 mm) in order to break the freeze-dried cake into small granules and thereby facilitating homogeneous mixing with the other excipients. First, the freeze-dried powder was gently mixed with Avicel® PH-101 by a spatula and transferred to a turbular mixer. Secondly, mannitol and Ac-Di-Sol® were added and mixed for 10 min. Finally, sodium stearyl fumarate was added and mixed for 2 min. The mixed powder was compressed to tablets as described in Section 6.4.6.

6.4.5 Preparation of sublingual tablets containing tacrolimus physical mixtures (PM)

The corresponding physical mixture was composed of tacrolimus as received and freeze-dried powder containing the carrier and Ac-Di-Sol®. The freeze-dried powder

Table 2 Formulation of sublingual tablets containing 1 mg tacrolimus.

Ingredients	Formulations			
	A	B	C	D
Freeze-dried powder of tacrolimus/Ac-Di-Sol®/carrier[a] (mg)	40[b]	20[c]	10[d]	–
Tacrolimus physically mixed with freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa (mg)	–	–	–	10[e]
Avicel® PH-101 (mg)	21.625	41.625	51.625	51.625
Mannitol (mg)	10	10	10	10
Ac-Di-Sol® (mg)	3	3	3	3
Sodium stearyl fumarate (mg)	0.375	0.375	0.375	0.375

[a] Carriers were inulin 1.8 kDa and 4 kDa, and PVP K30.
[b] Freeze-dried powder contained 2.5% w/w tacrolimus in carrier.
[c] Freeze-dried powder contained 5% w/w tacrolimus in carrier.
[d] Freeze-dried powder contained 10% w/w tacrolimus in carrier.
[e] Physical mixture powder contained 10% w/w tacrolimus in freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa.

was sieved through stainless steel sieve #30 and gently mixed with tacrolimus by a spatula. The powder mixture was mixed with the same excipients and the same amounts as shown in Table 2 prior to compression to tablets.

6.4.6 Tableting

Powder was compressed to flat, round tablets by using an ESH compaction apparatus (Hydro Mooi, Appingedam, The Netherlands). The tablet weight was 75 mg with diameter of 7 mm. The maximum force of 2 kN was reached in 2 s. The tablets were stored for at least one day in a vacuum desiccator over silica gel at room temperature before analysis.

6.4.7 Dissolution experiments

Dissolution of sublingual tablets of 1 mg tacrolimus was performed by using a USP dissolution apparatus II (Rowa Techniek, Leiderdorp, The Netherlands) with a paddle at 50 rpm and 37°C. Demineralized water (250 mL) containing 0.5% w/v SLS was used to maintain sink conditions. The samples (3 mL) were manually withdrawn through a 0.35 µm filter at given time intervals of 2, 5, 8, 10 and 15 min and were then replaced by fresh dissolution medium.

The samples were analyzed by high performance liquid chromatography (HPLC-UV). Measurements were conducted in triplicate. Amounts of drug dissolved are shown as average percentages with standard deviation bars.

6.4.8 HPLC analysis

Samples were analyzed by a method as described by Nishikawa et al. [14] with some modifications. The HPLC system consisted of a pump (Model 510; Waters Associates, Milford, MA, USA), an autosampler (Model 717 plus autosampler; Waters Associates), UV-detector (Model 783 Programmable Absorbance Detector; Applied biosystems, Foster City, CA, USA), a C18, 5 µm, 250 mm × 4.6 mm column (Nucleosil®, Macherey-Nagel GmbH&CO. KG, Düren, Germany) and an oven for warming the column (Model 7990, Jones Chromatography, Mid Glamorgan, UK). Sample injection volume was 150 µL. Detection wavelength was 210 nm. Column temperature was maintained at 60°C. The mobile phase consisted of acetonitrile/milli-Q water in a ratio of 7:3 (v/v) adjusted to pH 3.5 by using 3 M phosphoric acid. The flow rate was 0.8 mL/min. Tacrolimus retention time was approximately 11.8 min. Linearity range was from 0.50 to 20 µg/mL ($r^2 \geq 0.999$)

6.4.9 Comparison of dissolution profiles

Dissolution profiles were compared by using similarity factor (f_2), which is defined by the following equation [15]:

$$f_2 = 50 \log\{[1+1/n \Sigma n_{t=1}(R_t\text{-}T_t)^2]^{-0.5} \times 100\}$$

where n is the number of dissolution sampling times, and R_t and T_t are the percent dissolved at each time point for the reference and test products, respectively. An f_2 value higher than 50 indicates that the two dissolution profiles are similar.

6.4.10 Disintegration test

The disintegration time of tablets was determined in 900 mL demineralized water at 37°C using a USP disintegration test apparatus without disc (Erweka Apparatebau-GmbH, Heusenstamn Kr. Offenbach/Main, Germany). The samples were tested in triplicate.

6.4.11 Stability study of the product

Selected solid dispersions and sublingual tablets in closed vials were placed in climatic chambers at 20°C/45%RH and 40°C/75%RH for 6 months. Solid dispersions were subjected to X-ray powder diffraction. Furthermore, disintegration time, dissolution and drug content of sublingual tablets were tested.

6.5 RESULTS AND DISCUSSION

6.5.1 XRPD studies

XRPD patterns of tacrolimus, physical mixture of crystalline tacrolimus (10% w/w drug load) physically mixed with freeze-dried powder containing inulin 1.8 kDa and Ac-Di-Sol®, and the corresponding solid dispersions in which tacrolimus incorporated in inulin 1.8 kDa and Ac-Di-Sol® are shown in Fig. 1. Tacrolimus from the physical mixture showed the typical diffraction peaks in agreement with the diffraction peaks of pure tacrolimus. This indicates that no change in the physical state of tacrolimus physically mixed with the freeze-dried carrier. In contrast, the solid dispersions did not show any characteristic diffraction peaks of crystalline tacrolimus indicating that the drug was amorphous. XRPD patterns of all other solid dispersions also indicate that tacrolimus was full amorphous in these solid dispersions (data not shown). Differential scanning calorimetry (DSC) is a common method to determine the physical state of solid dispersions. However, since the melting point of tacrolimus (about 130°C) and glass transition temperatures of the carriers (about 130°C-170°C) are in the same temperature range [16]. DSC is not a suitable method to determine the physical state of tacrolimus in these carriers. Therefore, DSC measurements were not used in this study.

6.5.2 SEM studies

SEM pictures of crystalline tacrolimus, Ac-Di-Sol®, inulin 1.8 kDa, freeze-dried powder of 10% w/w tacrolimus incorporated in inulin 1.8 kDa and Ac-Di-Sol®, and the corresponding physical mixture are shown in Fig. 2a-e. Crystalline tacrolimus had an irregular shape. Ac-Di-Sol® showed a fibrous nature yielding a disintegrating property by water wicking [17]. Inulin 1.8 kDa showed the spherical shape particles with some fragments because it was produced by spray drying [18]. However, when producing

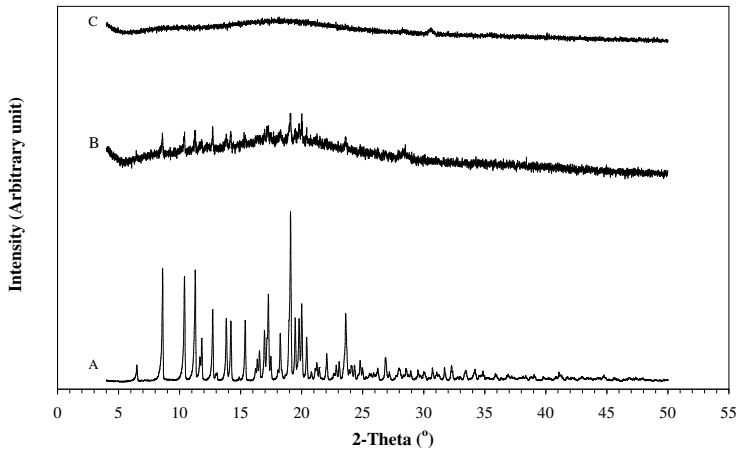

Figure 1 X-ray powder diffraction patterns of (A) tacrolimus, (B) tacrolimus (10% w/w) physically mixed with freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa and (C) freeze-dried powder of tacrolimus (10% w/w) incorporated in Ac-Di-Sol® and inulin 1.8 kDa.

the freeze-dried powder containing these compounds, the physical appearance of the powder was completely different from that of the original materials. The morphology of the freeze-dried powder showed a lack of intact crystalline tacrolimus and presence of a porous structure. Finally, the physical mixture of crystalline tacrolimus physically mixed with freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa showed that drug particles did not attach to the carrier after mixing implying no interactive mixture.

6.5.3 Dissolution studies of tacrolimus sublingual tablets

The dissolution behavior of tablets (Formulation A, B and C) containing the ingredients as presented in Table 2 was investigated. The superdisintegrant Ac-Di-Sol® was incorporated in the solid dispersions and mixed with the solid dispersions to facilitate the disintegration and thereby rapid dissolution of the tablets [19]. Mannitol was used because it has a cooling effect with a sweet taste. Avicel® PH-101 was used as a filler binder and sodium stearyl fumarate as a lubricant.

6.5.3.1 Different carriers and drug loads

Dissolution of sublingual tablets containing solid dispersions with tacrolimus at a drug load of 2.5% w/w incorporated in inulin 1.8 kDa, 4 kDa or PVP K30 (Formulation A) are presented in Fig. 3a. The formulation containing inulin 1.8 kDa-based solid dispersions allowed faster dissolution rate of tacrolimus than those containing inulin 4 kDa- or PVP K30-based solid dispersions. At 2 min, the drug was dissolved for about 15% from PVP K30, 36% from inulin 4 kDa and 45% from inulin 1.8 kDa. At 15 min, only formulation containing inulin 1.8 kDa-based solid dispersions yielded complete drug dissolution. Moreover, the similarity factor (f_2) was used to compare dissolution

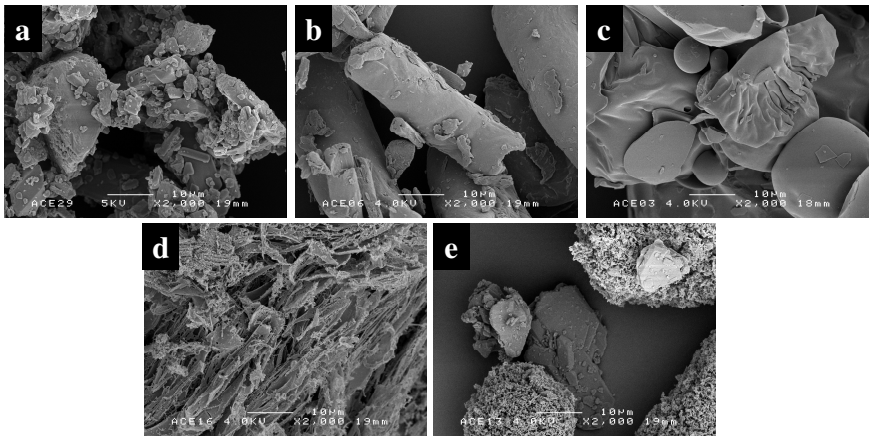

Figure 2 SEM pictures of (**a**) tacrolimus, (**b**) Ac-Di-Sol®, (**c**) inulin 1.8 kDa, (**d**) freeze- dried powder of tacrolimus (10% w/w) incorporated in Ac-Di-Sol® and inulin 1.8 kDa, and (**e**) tacrolimus (10% w/w) physically mixed with freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa.

profiles. As shown in Table 3, all the f_2 values were less than 50, indicating dissimilar dissolution profiles.

The dissolution of sublingual tablets containing solid dispersions with a drug load increased to 5% w/w is illustrated in Fig. 3b. For each carrier, the dissolution rate increased as compared to that of the tablets containing solid dispersions with a drug load of 2.5% w/w. At 2 min, the dissolution of drug from inulin 1.8 kDa was highest, followed by from inulin 4 kDa and PVP K30, respectively. In addition, at 15 min, the drug was dissolved for about 90% from inulin 4 kDa or PVP K30 and about 100% from inulin 1.8 kDa. These results are in agreement with the f_2 values as presented in Table 3. The f_2 values suggest that dissolution profile of sublingual tablets containing inulin 4 kDa- or PVP K30-based solid dispersions was dissimilar to that containing inulin 1.8 kDa-based solid dispersions.

Finally, as can be seen in Fig. 3c, when the drug load in solid dispersions was increased to 10% w/w, the dissolution behavior of sublingual tablets (Formulation C) from three different carriers was not significant different. The drug was dissolved fast in the beginning of dissolution profiles and after 15 min the amount of drug dissolved was over 90%. The f_2 values as shown in Table 3 indicate the similar dissolution profiles for all formulations.

The influence of carrier type on dissolution behavior of drug was more pronounced when the drug load in solid dispersions was low. Tablets containing PVP K30-based solid dispersions dissolved slower than the tablets containing inulin-based solid dispersions. This seems in contrast to a previous study in which we showed that tablets composed of diazepam or nifedipine incorporated in PVP K30-based solid dispersions dissolved faster than those in inulin 4 kDa-based solid dispersions. This result was

Table 3 Similarity factor (f_2) for dissolution profiles of sublingual tablets with different carriers and drug loads.

	Formulation A[a] 2.5% w/w drug load		**Formulation B[a] 5% w/w drug load**		**Formulation C[a] 10% w/w drug load**	
Carriers	Inulin 1.8 kDa	Inulin 4 kDa	Inulin 1.8 kDa	Inulin 4 kDa	Inulin 1.8 kDa	Inulin 4 kDa
Inulin 1.8 kDa	–	–	–	–	–	–
Inulin 4 kDa	24	–	43	–	56	–
PVP K30	18	40	33	54	51	60

[a] Compositions of formulation A, B and C are presented in Table 2.

explained by the fact that PVP K30 interacts with the drugs resulting in an increased dissolution rate of drug; whereas inulin 4 kDa shows no interaction with the drugs [16]. However, in another study, Primojel® was incorporated as a superdisintegrant in solid dispersions composed of fenofibrate and PVP K30 or inulin 4 kDa. The dissolution of inulin 4 kDa-based solid dispersion tablets was superior to that of PVP K30-based solid dispersion tablets [19]. For both Ac-Di-Sol® and Primojel® strong swelling is an important part of their mechanism of promoting disintegration. Apparently, this disintegration mechanism applies particularly to inulin-based solid dispersions and not to PVP K30-based solid dispersions. A superdisintegrant with a strong swelling property acts better for less water-soluble carrier rather than for more water-soluble carrier [20]. Accordingly, since the aqeous solubility of PVP K30 [21] is much higher than that of inulin 1.8 kDa or inulin 4 kDa [22], dissolution of the sublingual tablets containing PVP K30-based solid dispersions is therefore slower than that containing inulin-based solid dispersions.

At a drug load of 2.5% and 5% w/w, the inulin 1.8 kDa-based solid dispersion tablets dissolved faster than the inulin 4 kDa-based solid dispersion tablets which can be attributed to the fact that due to its lower molecular weight inulin 1.8 kDa has a higher aqueous solubility than inulin 4 kDa [22].

However, when the drug load in the solid dispersions was increased to 10% w/w, the differences of dissolution profiles among the carriers were less pronounced. As can be seen in Table 2, a higher drug load in the solid dispersions led to an increased amount of Avicel® PH-101 in the formulation in order to keep the tablet weight constant. Since Avicel® PH-101 causes penetration of water into the tablets by capillary forces, the disintegration of the tablets was faster. Accordingly, it is concluded that the dissolution behavior of sublingual tablets containing freeze-dried powder with a low drug load was predominantly determined by the dissolution of carrier. An increased amount of Avicel® PH-101 in the sublingual tablets masked the influence of the carrier.

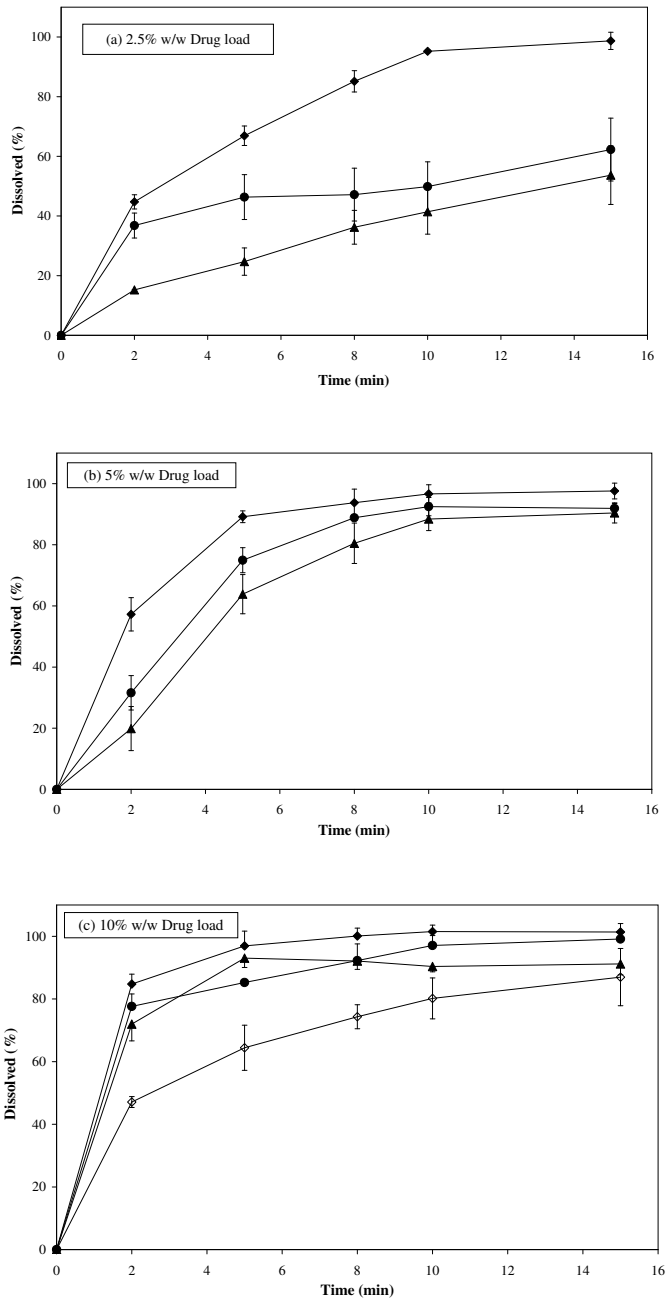

Figure 3 Dissolution of sublingual tablets from the formulation containing freeze-dried powder with different carriers and drug loads (**a**) 2.5% w/w, (**b**) 5% w/w and (**c**) 10% w/w (♦: inulin 1.8 kDa , ●: inulin 4 kDa ,▲: PVP K30 and ◊: Formulation containing tacrolimus (10% w/w) physically mixed with freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa) (data shown as mean values with standard deviation error bars).

Furthermore, the dissolution of sublingual tablets containing crystalline tacrolimus (10% w/w) physically mixed with Ac-Di-Sol®/inulin 1.8 kDa freeze-dried powder and the other excipients (Formulation D) is shown in Fig. 3c. As expected, the dissolution rate of the drug was slower than the sublingual tablets containing freeze-dried powder (Formulation C). This confirms that amorphous drug yielded a higher dissolution rate than its crystalline counterpart. In addition, as shown in SEM micrographs (Fig. 2d-e), the particle size of drug in the solid dispersions is likely to be much smaller than in the physical mixtures, leading to the higher dissolution rate.

6.5.3.2 Storage studies

The sublingual tablets containing solid dispersions of 10% w/w tacrolimus incorporated in Ac-Di-Sol®/inulin 1.8 kDa were selected for the stability study. The solid state of the drug incorporated in the solid dispersions after storage at 20°C/45%RH and 40°C/75%RH for 6 months was investigated by XRPD. In addition, the dissolution behavior, disintegration time and the drug content were determined.

The XRPD patterns of the inulin 1.8 kDa-based solid dispersions with 10% w/w tacrolimus stored at those conditions are shown in Fig. 4. None of characteristic peaks of crystalline tacrolimus was found in the diffractograms which indicate that tacrolimus in solid dispersions did not crystallize during storage under these conditions and remained fully amorphous.

As shown in Fig. 5, the tablets still dissolved fast after storage. Their dissolution profiles showed the similarity to the dissolution profile of freshly prepared tablets (f_2 > 50). Moreover, disintegration time of these tablets after storage was not significant

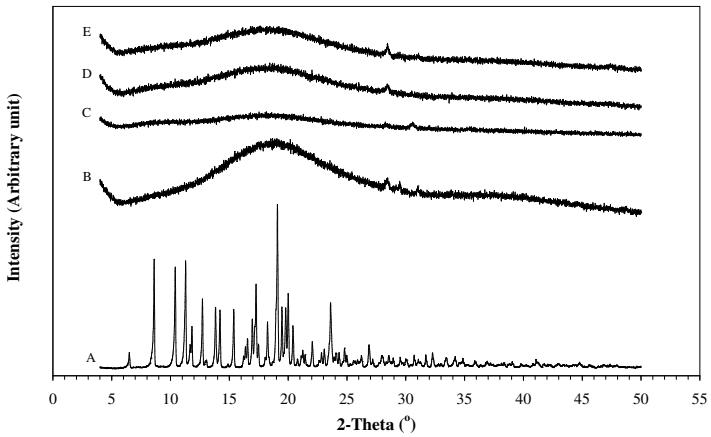

Figure 4 X-ray powder diffraction patterns of (A) tacrolimus, (B) freeze-dried powder of Ac-Di-Sol® and inulin 1.8 kDa, and freeze-dried powders of tacrolimus (10% w/w) incorporated in Ac-Di-Sol® and inulin 1.8 kDa at (C) freshly prepared, (D) 40°C/75%RH for 6 months, and (E) 20°C/45%RH for 6 months.

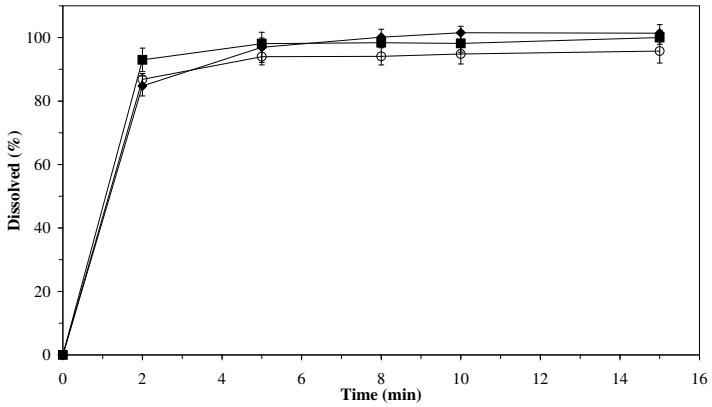

Figure 5 Dissolution of sublingual tablets from the formulation containing freeze-dried powder of tacrolimus (10% w/w) incorporated in inulin 1.8 kDa at ♦: freshly prepared, ○: 40°C/75%RH for 6 months and ▪: 20°C/45%RH for 6 months (data shown as mean values with standard deviation error bars).

different ($p > 0.05$) to that of the freshly prepared tablets (Table 4). These results indicate good physical stability of the tablets.

The drug content of the tablets did not decrease after storage at 20°C/45%RH for 6 months (Table 4) indicating good chemical stability. However, after storage at 40°C/75%RH for 6 months, the drug content was slightly but significantly ($p < 0.05$) decreased. Since conventional end-of-shelf-life specifications are 90-110% of the labeled claim [23], the remained drug content of about 95% is acceptable. The slightly decreased drug content is probably attributed to hydrolysis and/or thermal degradation as previously reported [24]. Therefore, we recommend not to store the tablets at elevated temperatures.

Table 4 Drug content and disintegration time of sublingual tablets containing freeze-dried powder of 10% w/w tacrolimus incorporated in Ac-Di-Sol®/inulin 1.8 kDa (Formulation C), and similarity factor (f_2) for dissolution profiles of the sublingual tablets freshly prepared and at storage conditions for 6 months.

Tests		Storage conditions	
	Freshly prepared	20°C/45%RH	40°C/75%RH
Drug content (% labeled amount)	99.33 ± 0.74	98.18 ± 1.11	94.82 ± 0.91
Disintegration time (second)	35.7 ± 3.8	34.0 ± 3.5	24.7 ± 7.8
Similarity factor (f_2)[a]	–	69	65

[a] Comparison of dissolution profiles between the sublingual tablets, freshly prepared versus stored tablets.

6.6 CONCLUSION

The tacrolimus solid dispersions produced by the freeze drying method yield a fully amorphous drug incorporated in the carriers. The formulation of sublingual tablets by using inulin 1.8 kDa as a carrier in solid dispersions allows the faster dissolution behavior, compared with inulin 4 kDa or PVP K30. The sublingual tablets containing 10% w/w drug load incorporated in inulin 1.8 kDa, and the other excipients yields a satisfied dissolution behavior and an excellent stability at 20°C/45%RH for 6 months. This formulation is therefore proposed for use in further clinical studies.

ACKNOWLEDGEMENTS

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CHAPTER 7

SUMMARY, CONCLUDING REMARKS AND PERSPECTIVES

7.1 SUMMARY

Solid dispersions can be used to improve the dissolution behavior of Biopharmaceutical Classification System class II and IV drugs and thereby their bioavailability after oral administration. In this thesis, research is described that clearly shows that the choice of the type of carrier, the physico-chemical properties of a specific polymeric carrier, the drug load, the type of drug, and presence and way of incorporation of additives strongly affect the dissolution behavior of solid dispersion tablets.

Chapter 2 contains a review on the different methods that are currently used to produce solid dispersions. In addition, the physico-chemical characteristics of differently produced dispersions are described.

In **Chapter 3,** the effects of the type of carrier and the molecular weight of the carrier on the dissolution behavior of drugs from solid dispersion tablets were evaluated. Two types of carriers were used, i.e. inulin (1.8 kDa, 4 kDa and 6.5 kDa), and polyvinylpyrrolidone (PVP K12, K30 and K60). Diazepam and nifedipine were used as model drugs. These drugs were incorporated in the carriers at different loads. All solid dispersions prepared were fully amorphous as determined by modulated differential scanning calorimetry (MDSC) and X-ray powder diffraction (XRPD). The solubility of the two drugs in all inulin solutions (10% w/v) was similar to that in demineralized water implying the absence of drug-carrier interactions. In contrast, the solubility of the drugs in all PVP solutions (10% w/v) was increased as compared to that in demineralized water indicating the presence of drug-carrier interactions. The dissolution rate of the drugs from all solid dispersions prepared was higher than that from the corresponding physical mixtures. At a relatively low drug load, both inulin and PVP based solid dispersion tablets dissolved fast. However, at a relatively high drug load, dissolution rate of the drugs from inulin-based solid dispersion tablets was lower than that from PVP-based solid dispersion tablets. This result correlates well with the solubility of the drugs in inulin or PVP solutions. During dissolution of a solid dispersion tablet with a high drug load, there will be a high drug concentration in the near vicinity of the dissolving tablet from which the drug can recrystallize. This may result in the formation of large crystals which obviously dissolve slowly. During dissolution, however, the carrier concentration in the near vicinity of the dissolving tablet will also be high. Due to the higher solubility of the drugs in the PVP solutions than in the inulin solutions, the drug will recrystallize at a lower drug load when inulin-based solid dispersion tablets are used compared to PVP-based solid dispersion tablets. Consequently, PVP-based solid dispersion tablets with a relatively high drug load allowed a faster dissolution.

In addition, with increasing molecular weight the dissolution rate of the carrier will decrease. Consequently, the molecular weight of the carrier affected the dissolution rate of the drug. The dissolution behavior of tablets prepared from solid dispersions with diazepam (20% w/w) incorporated in different molecular weights of PVP (K12,

K30 and K60) was studied. The PVP K12-based solid dispersion tablets showed a fast dissolution of PVP but a slow dissolution of diazepam. The slow dissolution of diazepam can be explained by the fact that it crystallizes in the near vicinity of the dissolving tablet because of the very high dissolution rate of PVP K12. On the other hand, PVP K30-based solid dispersion tablets exhibited a fast dissolution of both PVP and diazepam and both components dissolved at the same rate. The dissolution rate of PVP K30, however, was lower than that of PVP K12. Apparently, due to the somewhat slower dissolution rate of PVP K30 as compared to PVP K12, the concentration of the drug in the near vicinity of the dissolving tablet was lower by which recrystallization of the drug did not occur resulting in a higher dissolution rate. Also both components of the PVP K60-based solid dispersion dissolved at the same rate. However, the dissolution rate was very slow. It can be concluded that also in this case, the drug did not crystallize during dissolution. However, because the carrier dissolved very slow, the drug also dissolved very slow. Inulin-based solid dispersion tablets showed a similar behavior.

In conclusion, fast dissolution of drug incorporated in carriers at a relatively high drug load is obtained when a carrier is used which interacts with the drug. The dissolution rate of drugs from solid dispersion tablets is governed by both the drug load and the dissolution rate of the carrier.

In **Chapter 4**, the effect of the incorporation of superdisintegrants in solid dispersion tablets on the dissolution behavior was investigated. Various carriers (inulin 4 kDa, PVP K30, polyethylene glycol 20 kDa (PEG 20K), hydroxypropyl-β-cyclodextrin (HPβCD) and mannitol) and superdisintegrants (Primojel®, Ac-Di-Sol®, Polyplasdone® XL, and Polyplasdone® XL-10) were evaluated. The superdisintegrants were incorporated at a concentration of 4% w/w and in all cases fenofibrate was used as a model drug. The drug was incorporated in the solid dispersion tablets at a high drug load (about 50%). DSC and XRPD measurements indicated that incorporated fenofibrate was predominantly crystalline in all solid dispersions.

First, the effect of the mode of superdisintegrant (i.e. Primojel®) incorporation in the solid dispersion tablets (solid dispersions based on inulin 4 kDa) on the dissolution rate of fenofibrate was investigated. The dissolution rate of the drug was increased in the order: tablets prepared from a solid dispersion without superdisintegrant incorporated < tablets prepared from a physical mixture of superdisintegrant and solid dispersion < tablets prepared from a solid dispersion with the superdisintegrant incorporated. Therefore, in further experiments solid dispersions in which the superdisintegrant was incorporated were used. The effect of the type of superdisintegrant on the dissolution behavior of inulin 4 kDa-based solid dispersion tablets was examined. The dissolution rate of the drug was increased in the order: Polyplasdone®XL-10 < Polyplasdone®XL << Ac-Di-Sol® ≈ Primojel®. Also the effect of the type of carrier (inulin 4 kDa, PVP K30, PEG 20K, HPβCD and mannitol) on dissolution behavior of solid dispersions with Primojel® incorporated was investigated. Dissolution rate of the drug was increased in the order: mannitol < HPβCD < PVP K30 < PEG 20K < inulin 4 kDa.

The disintegration time and dissolution rate of the drug correlated well when different superdisintegrants were incorporated in solid dispersions containing the same carrier (inulin 4 kDa). In contrast, this correlation was not found with a superdisintegrant (Primojel®) incorporated in solid dispersions containing different carriers. The absence of this correlation might be due to the specific characteristics of the different carriers (e.g. solubility, compactability) and/or the size of the drug particles formed in the solid dispersions.

Furthermore, the dissolution profile of the inulin 4 kDa-based solid dispersion tablets with Ac-Di-Sol® or Primojel® incorporated stored at 20°C/45%RH and 40°C/75%RH for 3 months was similar to that of the corresponding freshly prepared tablets. Finally, inulin 4 kDa-based solid dispersion with Primojel® incorporated was physically mixed with Avicel® PH-102 and then compressed into tablets. The dissolution profile of the tablet formulation was similar to that of a marketed tablet containing fenofibrate nanocrystals (Lipanthyl®).

In conclusion, incorporation of superdisintegrant in the carrier is a promising strategy to enhance dissolution rate of drug particularly for the solid dispersions with a high drug load.

In **Chapter 5**, the applicability of Inutec® SP1 as a carrier for solid dispersion was compared to native inulin 2.3 kDa and PVP K30. Hereto, the physicochemical properties of the pure carrier and the dissolution behavior of the drugs (diazepam, fenofibrate, ritonavir and efavirenz) from tablets prepared from solid dispersions containing these carriers were investigated.

The surface tension measurements indicated that Inutec® SP1 was surface active and a critical micelle concentration of 0.009% w/v was found. In contrast, native inulin 2.3 kDa and PVP K30 were not surface active. The solubility of the four drugs in pure water and in aqueous solutions containing the different carriers increased in the order: pure water ≈ inulin 2.3 kDa containing solutions < PVP K30 containing solutions << Inutec®SP1 containing solutions. These results indicate that the drugs do not interact with native inulin 2.3 kDa, moderately interacts with PVP K30 and strongly interact with Inutec® SP1.

Solid dispersions were prepared by spray freeze drying. MDSC measurements revealed that diazepam, ritonavir and efavirenz were incorporated in the solid dispersions in the amorphous state for all three carriers. Fenofibrate on the other hand was incorporated in the carriers predominantly in the amorphous state. However, a small fraction of fenofibrate was crystalline. The relative crystallinity of fenofibrate in the different carrier-based solid dispersions increases in the order: PVP K30 < Inutec® SP1 ≈ inulin 2.3 kDa. Scanning electron microscopy showed that the spray freeze-dried powder consisted in all cases of small, spherical and highly porous particles with a similar morphology. The hygroscopicity of the different carrier-based solid dispersions and the corresponding physical mixtures was determined by dynamic vapor sorption measurements. As compared to the corresponding physical mixtures,

the amount of water absorbed by the solid dispersions was similar for native inulin 2.3 kDa, slightly decreased for Inutec® SP1 and strongly decreased for PVP K30. These results imply that native inulin 2.3 kDa does not interact with the drugs which is in agreement with the solubility data. In contrast, based on these results Inutec® SP1 only seems to interact slightly with the drugs which is not in agreement with the solubility data. However, Inutec® SP1 consists of a hydrophilic part which can absorb large amounts of water and a hydrophobic part which can only absorb small amounts of water. Since the drug will interact with the hydrophobic part of the molecule, this interaction will not or hardly affect the amount of water adsorbed. The vapor sorption measurements indicate that PVP K30 strongly interacts with the drugs which is in agreement with the solubility data.

Overall, at a relatively high drug load, the dissolution rate of the drugs from Inutec® SP1-based solid dispersion tablets was higher than that from native inulin 2.3 kDa- or PVP K30-based solid dispersion tablets. The faster dissolution of Inutec® SP1-based solid dispersion tablets can be ascribed to the formation of Inutec®SP1 micelles at the near vicinity of the dissolving tablets. Dissolved drug molecules can be incorporated in these micelles by which the saturation concentration of the drug at the near vicinity of the dissolving tablet strongly increases. Consequently, the risk of recrystallization of the drugs is reduced. Furthermore, dissolution experiments indicate that Inutec® SP1-based solid dispersion tablets stored at 20°C/45%RH and 40°C/75%RH for 3 months were physically stable. Dissolution profile of the drugs at storage was comparable to that of the corresponding freshly prepared solid dispersion tablets.

In conclusion, Inutec® SP1 was shown to be a promising carrier for solid dispersions.

In **Chapter 6**, the development of a sublingual tablet containing the lipophilic drug tacrolimus is described. Solid dispersions were prepared by freeze drying using three different types of carriers (inulin 1.8 kDa, inulin 4 kDa, and PVP K30) and at three different drug loads (2.5%, 5% and 10% w/w). In addition, the superdisintegrant Ac-Di-Sol® at 4% w/w was incorporated in the solid dispersions in all cases. SEM and XRPD measurements indicated that all solid dispersions prepared were fully amorphous. Thereafter, all solid dispersions containing 1 mg tacrolimus were physically mixed with Ac-Di-Sol®, mannitol, sodium stearyl fumarate and Avicel® PH-101 and compressed into the tablets. The tablet weight of each formulation was kept constant at 75 mg by adjusting the amount of Avicel® PH-101. Dissolutions tests showed that the dissolution rate increased with increasing drug load of the solid dispersion. This result can be explained by the fact that when solid dispersions with higher drug load were used in the formulation of the tablets, the amount of solid dispersion was decreased to keep the amount of tacrolimus the same while the amount of Avicel® PH 101 was increased to keep the tablet weight constant. Avicel® PH-101 facilitated disintegration of the tablets. Therefore, with increasing amounts of Avicel® PH-101 in the tablet, the disintegration time decreased and the dissolution rate increased. Also, the type of carrier influenced the dissolution behavior of the tablets but only when the drug

load of the solid dispersions was relatively low (2.5% and 5% w/w). Dissolution rate of tacrolimus from the tablets containing the different carriers increased in the order: PVP K30 < inulin 4 kDa < inulin 1.8 kDa. However, at a relatively high drug load (10% w/w) the influence of the type of carrier was less pronounced. This was clearly caused by the fact that the drug from all three tablets dissolved extremely fast (about 80% within 2 min).

The tablet formulation containing the inulin 1.8 kDa-based solid dispersion with 10% w/w drug load was selected for a storage stability study. The dissolution behavior and disintegration time of the selected tablets stored at 20°C/45%RH and 40°C/75%RH for 6 months as compared to the corresponding freshly prepared tablets were not significantly different. The drug content of tablets stored at 20°C/45%RH was not decreased but after storage at 40°C/75%RH it was slightly decreased due to degradation of tacrolimus.

In conclusion, sublingual tablets containing inulin 1.8 kDa-based solid dispersions with 10% w/w drug load showed excellent dissolution behavior and stability at 20°C/45%RH and meet therefore the required qualifications for a clinical trial. However, to prevent degradation of the drug, the tablets should be not stored at high temperature or moist conditions.

7.2 CONCLUDING REMARKS AND PERSPECTIVES

In this thesis, several aspects of solid dispersions used to improve the dissolution rate of tablet formulations containing poorly soluble drugs have been investigated. Inulin is a oligosaccharide having a relatively high glass transition temperature (T_g) as compared to other saccharides such as trehalose or sucrose. Therefore, inulin is an interesting glass forming carrier for solid dispersions. Moreover the material may improve the stability of the drug. The applicability of inulin was compared with several other carriers such as polyvinylpyrrolidone (PVP) polyethylene glycol (PEG), hydroxypropyl-β-cyclodextrin (HPβCD) and mannitol.

Inulin-based solid dispersion tablets showed an improved dissolution rate of the drugs as compared to the corresponding physical mixtures. However, the ability of inulin-based solid dispersions to enhance the dissolution rate at higher drug loads is inferior to PVP-based solid dispersions. This is explained by the absence of interaction between the drug and inulin, leading to drug crystallization in the boundary layer adjacent to the dissolving solid dispersion. Incorporation of a superdisintegrant in the solid dispersion is a useful technique to improve dissolution rate of highly loaded solid dispersion tablets. The tablet will rapidly disintegrate due to the incorporation of a desintegrant by which crystallization of the drug will be prevented. Dispersing the superdisintegrant in the solution of drug-carrier prior to freeze-drying is a practical and efficient method to obtain a homogeneous distribution of the superdisintegrant in solid dispersion.

The type of carrier is a key factor determining the solid state of drugs in solid dispersions and thereby its dissolution behavior. An advantage of the non-interaction inulin over the interacting carrier PVP is the lower hygroscopicity of inulin. Therefore, the stability of inulin-based solid dispersions is better than that of PVP-based solid dispersions. In addition, other excipients in the formulation of the tablets will affect the dissolution rate of the drugs, for example through an improved disintegration behavior of the tablets.

Compared with native inulin, the surface-active derivative of inulin, Inutec® SP1, has the interesting property that it is able to interact with the incorporated drugs. The relatively large solubility enhancement of Inutec® SP1 results in an improved dissolution behavior of high drug load dispersions produced of Inutec® SP1 compared to inulin or even PVP. The versatility of Inutec® SP1 as carrier in solid dispersions was shown by applying Inutec® SP1 to several model drugs, which all showed an increased dissolution rate of the drugs. In addition, solid dispersions prepared from Inutec® SP1 were physically stable, possibly because of a low hygroscopicity.

Furthermore, in this thesis the development of a sublingual tablet containing an amorphous inulin-based solid dispersion with tacrolimus is described. The application of superdisintegrant in the dispersion allowed for a high drug load, which in turn provided sufficient "formulation space" to optimize the final product to a fast disintegrating and dissolving tablet with sufficient stability. In the near future, it would be very challenging to subject the sublingual tablets of tacrolimus to clinical trails and investigate whether this product has an improved bioavailability compared to the currently used oral product.

The main methods used for preparing the solid dispersions described in this thesis were freeze drying or spray freeze drying. However, other processes (as described in chapter 2) could have advantages with respect to aspects related to the industrial application as well as to the performance of the solid dispersions. Processes such as spray drying or hot melt extrusion may be easier to scale-up and provide improved process control compared to the freeze drying related methods. Therefore, it is interesting to prepare the solid dispersions using other methods such as spray drying. A major advantage of spray drying is a short process time and it yields a particulate product that can easily be further processed to the final product. However, different production methods could result in different physico-chemical properties of the solid dispersions. Therefore, investigations into different production processes should go hand-in-hand with investigations of the major characteristics of the solid dispersion. Especially the dissolution behavior, and the physical and chemical stability of the solid dispersions should be evaluated, since these are the most critical performance parameters of solid dispersions. An *in-line* analytical instrument for the physical state characterization of solid dispersions would be a powerful tool to gain a better understanding of unwanted changes in the product. The development of such a tool would increase the understanding of the behavior of the solid dispersion as well as of

the different effects that process changes may have. This would enable a more "quality-by-design" guided development of new products containing solid dispersions.

CHAPTER 8

SAMENVATTING, CONCLUSIES EN PERSPECTIEVEN

8.1 SAMENVATTING

Vaste dispersies kunnen worden toegepast om de oplossnelheid van BCS klasse II en IV geneesmiddelen te verhogen en daarmee de biologische beschikbaarheid van deze middelen na orale toediening te verbeteren. In dit proefschrift wordt onderzoek beschreven naar de verschillende aspecten die het oplosgedrag van tabletten gemaakt van vaste dispersies bepalen. De volgende aspecten zijn onderzocht: de keuze van de matrix, het molecuulgewicht van de matrix, de concentratie van het geneesmiddel, het type geneesmiddel, de aanwezigheid van additieven en de manier waarop deze worden ingesloten.

In **hoofdstuk 2** wordt een overzicht gegeven van de verschillende manieren waarop tegenwoordig vaste dispersies kunnen worden gemaakt. Ook worden de fysisch-chemische eigenschappen van vaste dispersies die op verschillende manieren worden gemaakt beschreven.

In **hoofdstuk 3** worden de effecten van het type matrix en het molecuulgewicht van de matrix op het oplosgedrag van geneesmiddelen uit tabletten die gemaakt zijn van vaste dispersies geëvalueerd. Twee typen matrices werden gebruikt, namelijk inuline (1,8 kDa, 4 kDa en 6,5 kDa) en polyvinylpyrrolidon (PVP K12, K30 en K60). Diazepam en nifidipine werden als modelgeneesmiddelen gebruikt. De geneesmiddelconcentratie in de vaste dispersies werd gevarieerd. Met modulated differential scanning calorimetry (MDSC) en X-ray powder diffraction (XRPD) kon worden vastgesteld dat alle gemaakte vaste dispersies volledig amorf waren. Verder werd aangetoond dat de oplosbaarheid van de twee geneesmiddelen in alle drie de inuline-oplossingen (10% w/v) en in gedemineraliseerd water vergelijkbaar was. Geconcludeerd werd dat de twee geneesmiddelen geen interactie vertonen met inuline. De oplosbaarheid van de twee geneesmiddelen in alle drie de PVP-oplossingen (10% w/v) was echter groter dan die in gedemineraliseerd water. Hieruit kan geconcludeerd worden dat de geneesmiddelen wel interacties vertonen met PVP. De geneesmiddelen in de tabletten die gemaakt waren van de vaste dispersies losten in alle gevallen sneller op dan de geneesmiddelen in tabletten die gemaakt waren van fysische mengsels met dezelfde samenstelling. Bij een relatief lage geneesmiddelconcentratie in de vaste dispersietabletten loste de geneesmiddelen snel op bij beide typen matrices. Bij een relatief hoge geneesmiddelconcentratie was de oplossnelheid van de geneesmiddelen van de vaste dispersietabletten met inuline als matrix echter veel lager dan die van de vaste dispersietabletten met PVP als matrix. Dit resultaat kan verklaard worden vanuit de oplosbaarheid van de geneesmiddelen in inuline- en PVP-oplossingen. Tijdens het oplossen van een vaste dispersietablet met een hoge geneesmiddelconcentratie zal de concentratie van het geneesmiddel in de directe omgeving van de oplossende tablet hoog zijn waardoor het kan uitkristalliseren. Hierdoor kunnen grote geneesmiddelkristallen ontstaan die vanzelfsprekend langzaam zullen oplossen. Tijdens het oplossen zal de concentratie van de matrix in de directe omgeving van de oplossende tablet echter ook hoog zijn. De oplosbaarheid van de

geneesmiddelen in een inuline-oplossing is lager dan in een PVP-oplossing. Daarom zal het geneesmiddel bij een lagere concentratie uitkristalliseren bij het oplossen vanuit een tablet met inuline als matrix dan bij het oplossen vanuit een tablet met PVP als matrix. Dit mechanisme verklaart waarom vaste dispersie tabletten met PVP als matrix met een relatief hoge geneesmiddelconcentratie toch nog snel oplossen.

Een matrix zal langzamer oplossen naar mate zijn molecuulgewicht toeneemt. Hierdoor zal het molecuulgewicht van de matrix de oplossnelheid van het ingesloten geneesmiddel beïnvloeden. Om dit nader te onderzoeken werd het oplosgedrag van vaste dispersietabletten met PVP K12, PVP K30 en PVP K60 als matrix en diazepam als geneesmiddel (20% w/w) met elkaar vergeleken. Bij de tabletten met PVP K12 als matrix loste de matrix zeer snel op maar het geneesmiddel zeer langzaam. Het langzame oplossen van het geneesmiddel kan worden verklaard uit het feit dat de matrix zo snel oplost dat de concentratie van het geneesmiddel in de directe nabijheid van de oplossende tablet zo hoog is dat het uitkristalliseert. Zoals eerder beschreven zullen de gevormde geneesmiddelkristallen vervolgens langzaam oplossen. De vaste dispersietabletten met PVP K30 als matrix vertoonden een heel ander oplosgedrag: zowel de matrix als het geneesmiddel losten snel op en beide componenten losten op met dezelfde snelheid. Verder werd waargenomen dat PVP K30 zoals verwacht enigszins langzamer oploste dan PVP K12. Kennelijk leidde het langzamere oplossen van PVP K30 ten opzichte van PVP K12 ertoe dat de concentratie van het geneesmiddel in de directe nabijheid van de oplossende tablet lager was waardoor het niet uitkristalliseerde en dus een hoge oplossnelheid werd verkregen. Ook beide componenten van de vaste dispersietablet met PVP K60 losten even snel op maar de oplossnelheid was erg laag. Ook in dit geval kan worden geconcludeerd dat het geneesmiddel niet uitkristalliseerde tijdens het oplosproces. Echter, omdat de matrix erg langzaam oploste, loste het geneesmiddel ook langzaam op. Vaste dispersietabletten met inuline als matrix lieten een vergelijkbaar oplosgedrag zien.

Uit dit onderzoek kan geconcludeerd worden dat een vaste dispersietablet met een relatief hoge geneesmiddelconcentratie een snelle afgifte van het geneesmiddel laat zien indien het geneesmiddel interacties vertoont met de matrix. Verder kan geconcludeerd worden dat de oplossnelheid van geneesmiddelen uit vaste dispersietabletten bepaald word door zowel de geneesmiddelconcentratie in de tablet als de oplossnelheid van de matrix.

In **hoofdstuk 4** werd het effect van het insluiten van superdesintegrantia in vaste dispersietabletten op het oplosgedrag onderzocht. Hierbij werden verschillende matrices (inuline 4 kDa, PVP K30, polyethyleenglycol 20 kDa (PEG 20K), hydroxypropyl-β-cyclodextrine (HPβCD) en mannitol) en superdesintegrantia (Primojel®, Ac-Di-Sol® en Polyplasdone® XL en Polyplasdone® XL-10) geëvalueerd. In alle gevallen was de concentratie van de superdesintegrantia in de tabletten 4% w/w en werd fenofibraat als modelgeneesmiddel gebruikt. De tabletten bevatten allen een hoge concentratie geneesmiddel (ongeveer 50% w/w). Met DSC en XRPD metingen kon

worden aangetoond dat het fenofibraat ingesloten in de vaste dispersies in alle gevallen voor het grootste deel kristallijn was.

Allereerst werd het effect van de wijze waarop de superdesintegrant (Primojel®) in de vaste dispersietablet (vaste dispersies met inuline 4 kDa als matrix) was ingesloten op het oplosgedrag onderzocht. Gevonden werd dat de oplossnelheid van het geneesmiddel toenam in de volgorde: tabletten gemaakt van vaste dispersies zonder dat er een superdesintegrant was ingesloten < tabletten gemaakt van een fysisch mengsel van de superdesintegrant en vaste dispersies < tabletten gemaakt van vaste dispersies waarin een superdesintegrant was ingesloten. Vanwege deze resultaten werden in verdere experimenten alleen vaste dispersies gebruikt waarin een superdesintegrant was ingesloten. Vervolgens werd het effect van het type superdisintegrant op het oplosgedrag van vaste dispersietabletten met inuline 4 kDa als matrix onderzocht. Hierbij werd gevonden dat de oplossnelheid van het geneesmiddel toenam in de volgorde: Polyplasdone® XL-10 < Polyplasdone® XL << Ac-Di-Sol® ≈ Primojel®. Daarnaast werd ook het effect van het type matrix (inuline 4 kDa, PVP K30, PEG 20K, HPβCD en mannitol) op het oplosgedrag van vaste dispersietabletten waarin Primojel® was ingesloten bestudeerd. Hierbij werd gevonden dat de oplossnelheid van het geneesmiddel toenam in de volgorde: mannitol < HPβCD < PVP K30 < PEG 20K < inuline 4 kDa.

Als de desintegratietijd en de oplossnelheid van vaste dispersies tabletten met hetzelfde type matrix (inuline 4 kDa), maar waarin verschillende superdesintegrantia waren ingeloten, met elkaar vergeleken worden, wordt een goede correlatie gevonden. Deze correlatie kon echter niet worden gevonden als vaste dispersietabletten waarin één specifieke superdesintegrant (Primojel®) was ingesloten, maar waarin verschillende matrices zaten, met elkaar vergeleken werden. De afwezigheid van deze correlatie zou toegeschreven kunnen worden aan de specifieke eigenschappen van de verschillende matrices (zoals oplosbaarheid, compactiegedrag) en/of de grootte van de geneesmiddeldeeltjes in de vaste dispersies.

Verder werd aangetoond dat het oplosgedrag van de vaste dispersietabletten met inuline 4 kDa als matrix, waarin Ac-Di-Sol® of Primojel® was ingesloten, niet veranderde tijdens opslag gedurende 3 maanden bij 20°C/45%RH of 40°C/75%RH. Tenslotte werden tabletten gemaakt van een fysisch mengsel van een vaste dispersie op basis van inuline 4 kDa met Primojel® en Avicel® PH-102. Het oplosprofiel van deze tablet was vergelijkbaar met dat van een commercieel verkrijgbaar nanokristal bevattende tablet (Lipanthyl®).

Geconcludeerd kan worden dat het insluiten van een superdisintegrant in een vaste dispersie een veelbelovende strategie is om de oplossnelheid van geneesmiddelen te verbeteren met name bij een hoge geneesmiddelconcentratie in een vaste dispersie.

In **hoofdstuk 5** werd de toepasbaarheid van een gederivatiseerde inuline, Inutec® SP1, als matrix voor vaste dispersies vergeleken met niet-gederivatiseerd inuline 2,3 kDa en PVP K30. Hiertoe werden de fysisch-chemische eigenschappen onderzocht

van de matrices en het oplosgedrag van tabletten vervaardigd van vaste dispersies met deze matrices waarin verschillende geneesmiddelen (diazepam, fenofibraat, ritonavir en efavirenz) waren ingesloten.

Oppervlaktespanningmetingen toonden aan dat Inutec® SP1 oppervlakteactief is en er werd een kritische micelconcentratie van 0.009% w/v gevonden. Het niet-gederivatiserde inuline and PVP K30 waren daarentegen niet oppervlakteactief. De oplosbaarheid van de vier geneesmiddelen in zuiver water en in waterige oplossingen van de verschillende matrices nam toe in de volgorde: zuiver water ≈ niet-gederivatiseerd inuline 2,3 kDa < PVP K30 << Inutec® SP1. Deze resultaten geven aan dat de geneesmiddelen geen interactie vertonen met niet-gederivatiseerd inuline 2,3 kDa, een matige interactie vertonen met PVP K30 en een sterke interactie vertonen met Inutec® SP1.

Vaste dispersies werden vervaardigd met behulp van sproeivriesdrogen. Met MDSC metingen kon worden aangetoond dat diazepam, ritanovir en efavirenz in de amorfe toestand waren ingesloten in alle drie de verschillende matrices. Fenofibraat was voor het grootste deel in de amorfe toestand insloten. Een klein deel van fenofibraat was echter kristallijn. De relatieve kristalliniteit van fenofibraat ingesloten in de vaste dispersies met de verschillende matrices nam toe in de volgorde: PVP K30 < Inutec® SP1 ≈ niet-gederivatiseerd inuline 2,3 kDa. Foto's gemaakt met een 'scanning electron microscope' lieten zien dat het gesproeivriesdroogde poeder in alle gevallen bestond uit kleine, bolvormige en zeer poreuze deeltjes met een vergelijkbare morfologie. De hygroscopiciteit van de vaste dispersies met de verschillende matrices en fysische mengsels met dezelfde samenstelling werd bepaald middels 'dynamic vapor sorption' (DVS) metingen. Gevonden werd dat, vergeleken met de fysische mengsels met dezelfde samenstelling, de hoeveelheid water geabsorbeerd door de vaste dispersies vergelijkbaar was voor niet-gederivatiseerd inuline 2,3 kDa, enigszins verminderd was voor Inutec® SP1 en sterk afgenomen was voor PVP K30. Deze resultaten tonen aan dat niet-gederivatiseerd inuline 2,3 kDa geen interacties vertoont met de geneesmiddelen, hetgeen in overeenstemming is met de vergelijkbare oplosbaarheid van de geneesmiddelen in zuiver water en in waterige oplossing van niet-gederivatiseerd inuline 2,3 kDa. De DVS metingen lijken daarentegen aan te geven dat Inutec® SP1 slechts beperkt interacties kan aangaan met de geneesmiddelen terwijl de oplosbaarheid van de geneesmiddelen in de waterige Inutec® SP1 oplossing juist veel hoger was dan in zuiver water. Deze resultaten kunnen verklaard worden uit het feit dat Inutec® SP1 bestaat een hydrofiel deel dat grote hoeveelheden water kan absorberen en een hydrofoob deel dat slechts een kleine hoeveelheid water kan absorberen. Omdat het geneesmiddel interacties zal vertonen met het hydrofobe deel van het molecuul zal deze interactie nauwelijks of geen effect hebben op de hoeveelheid geabsorbeerd water. DVS metingen laten verder zien dat PVP K30 interacties kan aangaan met de geneesmiddelen hetgeen in overeenstemming is met de toegenomen oplosbaarheid van de geneesmiddelen in waterige PVP K30 oplossingen ten opzichte van die in zuiver water.

Dissolutie-experimenten lieten het algemene beeld zien dat, bij een relatief hoge geneesmiddelconcentratie in de vaste dispersies, de oplossnelheid van het geneesmiddel uit de vaste dispersietabletten met Inutec® SP1 als matrix hoger was dan die van vaste dispersietabletten met niet-gederivatiseerd inuline 2,3 kDa of PVP K30 als matrix. Het sneller oplossen van de vaste dispersietabletten met Inutec® SP1 als matrix kan worden toegeschreven aan de vorming van Inutec® SP1 micellen in de directe nabijheid van de oplossende tabletten. Opgeloste geneesmiddelmoleculen kunnen worden ingesloten in deze micellen waardoor de oplosbaarheid van het geneesmiddel in de directe nabijheid van de oplossende tabletten sterk toeneemt. Als gevolg hiervan zal de kans dat het geneesmiddel uitkristalliseert sterk worden gereduceerd.

Verder werd aan de hand van dissolutie-experimenten vastgesteld dat de vaste dispersietabletten met Inutec® SP1 als matrix fysisch stabiel zijn tijdens opslag bij 20°C/45%RH of 40°C/75%RH gedurende 3 maanden.

Geconcludeerd kan worden dat Inutec® SP1 een veelbelovende matrix is voor vaste dispersies.

In **hoofdstuk 6** wordt de ontwikkeling van een tablet voor de sublinguale toediening van tacrolimus beschreven. Vaste dispersies met drie verschillende matrices (inuline 1,8 kDa, inuline 4 kDa en PVP K30) en drie verschillende geneesmiddelconcentraties (2,5%, 5% en 10% w/w) werden vervaardigd door middel van vriesdrogen. Bovendien werd in alle gevallen het superdesintegratiemiddel, Ac-Di-Sol®, met een concentratie van 4% w/w ingesloten in de vaste dispersies. Met 'scanning electron microscopy' en XRPD kon worden aangetoond dat alle vervaardigde vaste dispersies volledig amorf waren. Vervolgens werden fysische mengsels van de vaste dispersies met Ac-Di-Sol®, mannitol, natrium stearyl fumaraat en Avicel® PH-101 gecompacteerd tot tabletten. Hierbij werden de hoeveelheden vaste dispersie en Avicel® PH-101 zodanig gekozen dat in alle gevallen de tabletten 1 mg tacrolimus bevatten en het tabletgewicht 75 mg was. Gevonden werd dat de oplossnelheid van het geneesmiddel toenam naarmate de geneesmiddelconcentratie in de vaste dispersie toenam. Dit resultaat kon verklaard worden uit het feit dat bij toenemende geneesmiddelconcentratie in de vaste dispersie de hoeveelheid vaste dispersie in de tablet afnam om de hoeveelheid tacrolimus in de tablet hetzelfde te houden en daarom de hoeveelheid Avicel® PH-101 toenam om het tabletgewicht hetzelfde te houden. Avicel® PH-101 versnelde de desintegratie van tabletten. Daarom zal bij een toenemende hoeveelheid Avicel® PH-101 in de tablet de desintegratietijd afnemen en de oplossnelheid toenemen. Ook het type matrix beïnvloedde de oplossnelheid van de tabletten, maar alleen in de gevallen waarbij de geneesmiddelconcentratie in de vaste dispersie relatief laag was (2,5% w/w en 5% w/w). De oplossnelheid van tacrolimus uit de tabletten met de verschillende matrices nam toe in de volgorde: PVP K30 < inuline 4 kDa < inuline 1,8 kDa. Bij een relatief hoge geneesmiddelconcentratie (10% w/w) waren de verschillen minder uitgesproken. De oorzaak hiervan was dat de drie verschillende tabletten allen zeer snel oplosten (ongeveer 80% binnen 2 minuten).

De tabletformulering met de vaste dispersie met inuline 1,8 kDa als matrix en een geneesmiddelconcentratie van 10% w/w werd geselecteerd voor een stabiliteitsstudie. Het oplosgedrag en de desintegratietijd van deze tabletten werd niet significant beïnvloed tijdens opslag bij 20°C/45%RH en 40°C/75%RH gedurende 6 maanden. Het gehalte aan tacrolimus in de tabletten was niet veranderd na opslag bij 20°C/45%RH maar enigszins verlaagd na opslag 40°C/75%RH door ontleding van het geneesmiddel.

Geconcludeerd kan worden dat sublinguaal tabletten vervaardigd van vaste dispersies met inuline 1,8 kDa en een geneesmiddelconcentratie van 10% w/w een zeer goed oplosgedrag vertonen en stabiel zijn tijdens opslag bij 20°C/45%RH. Deze tabletten voldoen hiermee aan de benodigde kwalificaties voor een klinische studie. Om ontleding te voorkomen, moeten de tabletten niet worden opgeslagen bij een hoge temperatuur of hoge vochtigheidgraad.

8.2 CONCLUSIES EN PERSPECTIEVEN

In dit proefschrift worden verschillende aspecten van vaste dispersies onderzocht. Vaste dispersies worden toegepast voor de formulering van tabletten met slecht oplosbare geneesmiddelen. Inuline is een oligosaccharide met een relatief hoge glasovergangstemperatuur ten opzichte van sacchariden zoals sucrose en trehalose. Inuline is daardoor een interessante glasvormende matrix voor vaste dispersies. Het materiaal zou bovendien de stabiliteit van geneesmiddelen kunnen verbeteren. De toepasbaarheid van inuline werd vergeleken met verschillende andere matrices zoals polyvinylpyrrolidon (PVP), polyethyleenglycol (PEG), hydroxypropyl-β-cyclodextrine (HPβCD) en mannitol.

Vaste dispersietabletten met inuline als matrix lieten een verbeterde oplossnelheid van het ingesloten geneesmiddel zien vergeleken met tabletten die vervaardigd waren van fysische mengsels met dezelfde samenstelling. Vaste dispersietabletten met inuline als matrix vertoonden echter een minder goed oplosgedrag dan vaste dispersietabletten met PVP als matrix. Dit kan verklaard worden door de afwezigheid van interacties tussen het geneesmiddel en de inuline waardoor het geneesmiddel kan uitkristalliseren in de directe nabijheid van de oplossende tablet. Het insluiten van een superdesintegrant in een vaste dispersie is een geschikte techniek om de oplossnelheid van vaste dispersietabletten met een hoge geneesmiddelconcentratie te verbeteren. Door het insluiten van een superdesintegrant in een vaste dispersie zullen de tabletten namelijk zeer snel uiteen vallen waardoor uitkristallisatie van het geneesmiddel voorkomen kan worden. Het dispergeren van de superdesintegrant in de oplossing van het geneesmiddel en matrix voor vriesdrogen is een praktische en efficiënte methode om een homogene verdeling van de superdesintegrant in de vaste dispersie te verkrijgen.

Het type matrix draagt in belangrijke mate bij aan de manier waarop het geneesmiddel in de vaste dispersie is ingesloten en daarmee aan het oplosgedrag. Een

voordeel van inuline, dat geen interacties kan aangaan met het geneesmiddel, boven PVP, dat juist wel interacties kan aangaan met het geneesmiddel, is dat inuline minder hygroscoop is. De stabiliteit van vaste dispersies met inuline als matrix is daardoor beter dan die van vaste dispersies met PVP als matrix. Verder zullen andere hulpstoffen in de tabletformulering de oplossnelheid van de geneesmiddelen beïnvloeden, bijvoorbeeld doordat de tabletten sneller desintegreren.

In tegenstelling tot niet-gederivatiseerd inuline, heeft Inutec® SP1 wel de mogelijkheid om interacties aan te gaan met geneesmiddelen die in de vaste dispersies waren ingesloten. Doordat Inutec® SP1 de oplosbaarheid van geneesmiddelen relatief sterk verhoogde, losten geneesmiddelen sneller op uit vaste dispersietabletten met Inutec® SP1 als matrix en waarin geneesmiddelen in een hoge concentratie waren ingesloten dan uit vaste dispersietabletten met niet-gederivatiseerd inuline of zelfs PVP als matrix. Dat Inutec® SP1 veelzijdig toe kan worden gepast als matrix werd aangetoond met vaste dispersietabletten met deze matrix waarin verschillende geneesmiddelen waren ingesloten: al deze tabletten losten zeer snel op. Verder werd aangetoond dat vaste dispersies met Inutec® SP1 als matrix fysisch stabiel waren wat mogelijkerwijs veroorzaakt werd door hun lage hygroscopiciteit.

Verder wordt in dit proefschrift de formulering van een tablet voor de sublinguale toediening van tacrolimus beschreven. Deze tablet bevatte een amorfe vaste dispersie verwerkt met inuline als matrix en waarin tacrolimus was ingesloten. Door de toevoeging van een superdesintegrant kon een vaste dispersie met een hoge geneesmiddelconcentratie worden vervaardigd, waardoor een relatief grote hoeveelheid hulpstoffen in de tablet kon worden verwerkt. Door gebruik te maken van de juiste hulpmiddelen kon een tablet worden geformuleerd die snel desintegreerde en oploste en die voldoende stabiel was. Een klinische studie waarin de biologische beschikbaarheid van deze sublinguale tablet en het orale product dat tegenwoordig wordt toepast met elkaar vergeleken wordt zou een uitdaging voor de nabije toekomst kunnen zijn.

In dit proefschrift werden vaste dispersies voornamelijk door middel van vriesdrogen en sproeivriesdrogen vervaardigd. Andere processen (zoals beschreven in hoofdstuk 2) zouden echter voordelen kunnen hebben ten aanzien van aspecten gerelateerd aan industriële toepassing alsmede aan het functioneren van vaste dispersies. Processen als sproeidrogen en smelt extrusie bij hoge temperaturen zouden gemakkelijker opschaalbaar en beter controleerbaar kunnen zijn dan vriesdrogen en daaraan gerelateerde processen. Het zou daarom interessant zijn om vaste dispersies te vervaardigen door middel van andere processen zoals sproeidrogen. Een belangrijk voordeel van sproeidrogen is dat de procestijd kort is en dat het poederdeeltjes oplevert die gemakkelijk verwerkt kunnen worden tot het uiteindelijke product. Het toepassen van andere productiemethoden zou echter kunnen leiden tot vaste dispersies met andere fysisch-chemische eigenschappen. Onderzoek naar andere productiemethoden zou daarom parallel moeten verlopen met onderzoek naar de belangrijkste eigenschappen

van vaste dispersies. Met name het oplosgedrag en de fysische en chemische stabiliteit zouden geëvalueerd moeten omdat deze eigenschappen het meest kritisch zijn voor de toepasbaarheid van vaste dispersies. Analytische instrumentatie waarmee de fysische toestand van vaste dispersies *in-line* gekarakteriseerd kan worden zou een goede ondersteuning kunnen zijn om ongewenste veranderingen van het product beter te kunnen begrijpen. Met de ontwikkeling van dergelijke instumentatie zou een beter begrip kunnen worden verkregen over het gedrag van vaste dispersies alsmede de effecten van de procesparameters hierop. Hierdoor zouden we in staat kunnen zijn om met behulp van een "quality-by-design" benadering producten te kunnen ontwikkelen waarin vaste dispersies zijn verwerkt.

APPENDIX

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CURRICULUM VITAE

Parinda Srinarong was born (3 December 1972) in Bangkok, Thailand. She graduated from Chiang Mai University, Chiang Mai, Thailand in 1995 with a bachelor's degree in pharmacy. She obtained her master of science in pharmacy from Chulalongkorn University, Bangkok, Thailand in 2000. For her professional experiences, she worked as a researcher at the Research and Development Institute, the Government Pharmaceutical Organization, Bangkok, Thailand in 1996-1998 and in 2001-2005. She received the scholarship from the Government Pharmaceutical Organization and the financial support from the Department of Pharmaceutical Technology and Biopharmacy for her PhD-study under the supervision of Prof. Dr. Henderik W. Frijlink and Dr. Wouter L.J. Hinrichs in 2006-2011. After finishing her PhD-study, she will go back to Thailand to continue her work at the Government Pharmaceutical Organization.

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